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## PATHOGENETIC MECHANISMS IN HEMOLYTIC ANEMIAS

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AND

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Because of the finding of hemolysins of the immune body type in 2 cases of acute (acquired) hemolytic anemia and because of their disappearance as the patients improved after splenectomy, the possibility was conceived that a hemolysin might be directly related to the development of the hemolytic process<sup>1</sup> Immune hemolytic serum, produced in rabbits by the injection of guinea pig erythrocytes, when injected in guinea pigs resulted in fulminating, acute and sub-acute hemolytic states dependent on the dose of serum injected<sup>2</sup> In both clinical patients and experimental animals spherocytosis and increased fragility of the erythrocytes in hypotonic solutions of sodium chloride were present and regressed as the process improved It was concluded (*a*) that hemolytic anemias are due to the activity of agents which can be generically called hemolysins and (*b*) that spherocytosis (and increased hypotonic fragility) are the result of the activity of various types of hemolytic agents, thus spherocytosis can be considered an indicator of the presence of hemolytic activity

More recently, Ham and Castle<sup>3</sup> proposed another explanation for the development of hemolytic anemia clinically and for our results with the use of immune hemolytic serum experimentally Their explanation is based on the theory that unusual erythrostasis—as the result of agglutination, increased viscosity or slowing of the circulation—is at the basis of many hemolytic processes Our results<sup>2</sup> in experimental animals were explained by these investigators by the action of “agglutinating antibodies” in the hemolytic serum, the erythrocytes becoming agglutinated, with resultant stasis and hemolysis That erythrocytes could be *directly* injured by the activity of various hemolytic or agglutinating agents was not seriously considered

Our recent experiments indicate that the erythrocyte—normally a biconcave disk—is actively injured by a variety of agents, “simple” hemolysins, “complex” hemolysins or simple agglutinins, with the result that it is rendered susceptible to

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From the Joseph H Pratt Diagnostic Hospital and the Blood Clinic and Laboratory of the Boston Dispensary

Read before the Section on Pathology and Physiology at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 6, 1941

1 Dameshek, W, and Schwartz, S O The Presence of Hemolysins in Acute Hemolytic Anemia, *New England J Med* **218** 75, 1938

2 Dameshek, W, and Schwartz, S O Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, *Am J M Sc* **196** 769, 1938

3 Ham, T H, and Castle, W B Studies on Destruction of Red Blood Cells Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, *Tr A Am Physicians* **55** 127, 1940

such major factors as complement activity and mechanical trauma Whereas in the experiments of Ham and Castle the emphasis was on the passive factor of stasis, our past and recent experiments have stressed the multiplicity of agents—immunologic, chemical and physical—which may actively injure the envelope of the red cell The exact role of the spleen in hemolytic anemia is still obscure, although our experience in certain clinical cases suggests that it may directly produce hemolysins rather than act as a simple mechanical organ of stasis Active extrasplenic production of hemolysins is also probable in certain cases of “symptomatic” hemolytic anemia <sup>4</sup>

In the present paper the role of various factors in the development of hemolysins is described The activities of a pure hemolysin (saponin), of a pure agglutinin (concanavalin A) and of complex hemolysins (immune hemolytic serum and silicic acid) have been studied with relation to stasis, mechanical fragility and hypotonic fragility, and the effects in experimental animals noted From the results of these experiments and other data a formulation of etiologic factors which may underlie the various hemolytic syndromes has been made

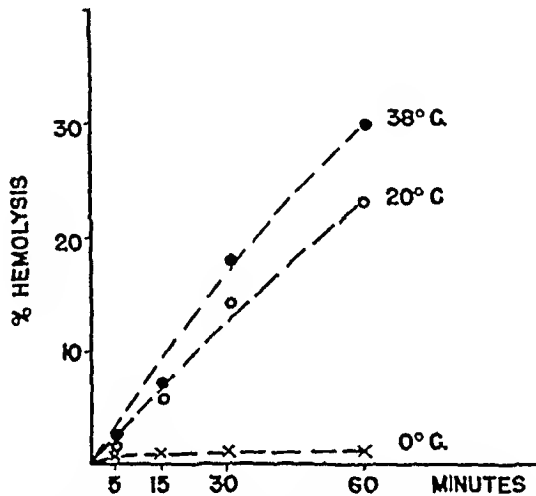


Fig 1—Rate of hemolysis with saponin 1:10,000 at various temperatures Saponin, a simple hemolysin, causes hemolysis without the aid of other factors Hemolysis is greatest at incubator temperature and practically nil at refrigerator temperature

#### EXPERIMENTAL OBSERVATIONS

*1 Saponin, a Simple Hemolysin*—Purified saponin (Merck), a powder, was dissolved in physiologic solution of sodium chloride, a 1:10,000 concentration ordinarily being used When this was kept in the refrigerator, a standard hemolytic activity against suspensions of human red cells containing 20,000,000 washed red cells per cubic centimeter of physiologic solution of sodium chloride was present for at least two weeks, although the precaution was observed of making up solutions at weekly intervals The rate and degree of hemolysis were observed by use of the Evelyn photoelectric colorimeter

The experiments were in general confirmatory of Ponder's <sup>5</sup> extensive experiments with this substance They showed that saponin acts directly on the erythrocyte without mediation of complement or other substances present in serum, that hemolysis is most marked at incubator temperature (fig 1) and that spherocytosis with greatly increased hypotonic fragility is present at subhemolytic levels of saponin concentration When the material was injected intravenously in rabbits in large doses, an acute hemolytic anemia with marked spherocytosis resulted, due apparently to the direct action of the drug on circulating erythrocytes

*2 Silicic Acid, a Complex Hemolysin*—Silicic acid was prepared by distillation from ethyl silicate One cubic centimeter of the heavy grayish liquid was mixed with 24 cc of distilled

<sup>4</sup> Singer, K, and Dameshek, W Symptomatic Hemolytic Anemia, *Ann Int Med* 15 544, 1941

<sup>5</sup> Ponder, E Effects of Simple Haemolysins in Hypotonic Systems, *Protoplasma* 27 523, 1937

water in a flask, heated directly over a small flame for hydrolysis and distilled for two hours in a reflux condenser. The silicic acid thus obtained was stored in the ice box. One cubic centimeter of this solution was mixed with 0.085 cc of a 10 per cent solution of sodium chloride and diluted in varying concentrations, 1:10, 1:20, etc., with physiologic solution of sodium chloride. The final dilutions, labeled 1:10, etc., were used in the experiments, to be described, against guinea pig red blood cells. Blood was obtained from guinea pigs by puncture of the heart. It was washed three times with physiologic solution of sodium chloride and suspended in 10 per cent concentration. Occasionally a 5 per cent suspension was used. Fresh guinea pig complement in 1:10 dilution was routinely used. The tests for hemolysis were usually performed in Hinton tubes (4 by  $\frac{3}{8}$  inches [10 by 0.95 cm]). The degree of hemolysis was determined by inverting the tubes once, centrifuging them for five minutes at high speed, removing 3 cc of the supernatant fluid, diluting this with 17 cc of 0.1 per cent solution of sodium carbonate and reading the Cenco photoelectric colorimeter for hemoglobin concentration, Cenco green filter no. 2 being utilized. The degree of hemolysis was readily ascertained from the hemoglobin reading.

**General Results** Silicic acid caused marked agglutination of guinea pig red cells in concentrations of 1:10 to 1:10,000. On the addition of guinea pig complement (1:10) to the agglutinated red cells, hemolysis took place immediately at the boundary between the complement and the red cells and gradually extended to the rest of the tube. Hemolysis was facilitated by incubation at 38 C and diminished at ice box temperature (0 C), as shown in figures 2 and 3.

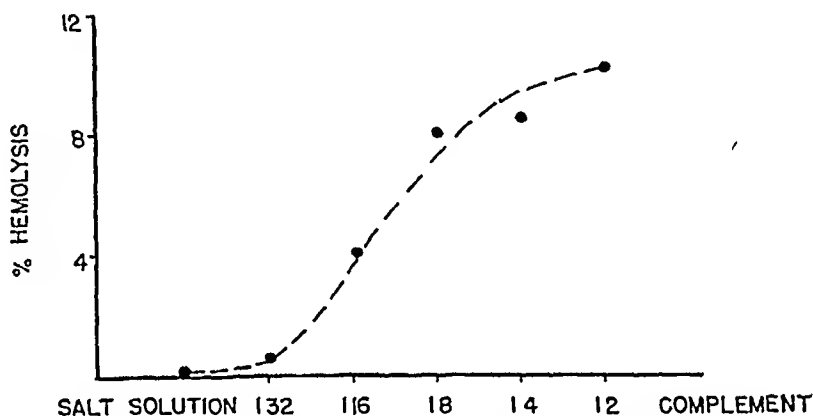


Fig 2—Hemolysis with colloidal silicic acid with added complement in various concentrations. Silicic acid, a complex hemolysin, without complement causes agglutination, with added guinea pig complement the degree of hemolysis is directly dependent on the concentration of complement. Complement is the actual hemolytic agent of cells already sensitized by silicic acid.

**Effects of Stasis on Sensitized Erythrocytes** Erythrocytes sensitized (i. e., agglutinated) by various concentrations of silicic acid (without complement) were observed at different temperatures for various periods and the degree of hemolysis noted. Although the results of these experiments varied from time to time, it was found that silicic acid in 1:10, 1:100, 1:1,000 and 1:10,000 concentrations caused agglutination of guinea pig red cells. When these cells were allowed to stand for forty-two hours at ice box temperature no hemolysis occurred, at room temperature for the same length of time there was questionable hemolysis, while at incubator temperature well marked hemolysis took place in the 1:10 concentration of silicic acid. There was slight hemolysis in the 1:100 concentration, but in the 1:1,000 and 1:10,000 concentrations there appeared to be an inhibition of hemolysis as compared with that of the control.

In other experiments, no essential change between the degree of hemolysis in the controls and in the sensitized cells occurred for seventeen and one-half hours, but at the nineteen hour interval a definite and well marked increase in hemolysis took place (fig 4), particularly in the higher concentrations. Suspensions of red cells made with isotonic 5.2 per cent dextrose solution instead of physiologic solution of sodium chloride showed definitely diminished hemolysis with stasis.

**Effect on Hypotonic Fragility** Erythrocytes sensitized (complement not used) by silicic acid were tested for their fragility in hypotonic solutions of sodium chloride. In one experiment, 12 cc of 1:100 silicic acid, 12 cc of 1:10 suspension of guinea pig red cells and 36 cc of physiologic solution of sodium chloride were mixed, the tubes inverted once, the agglutinated masses of red cells discarded, the rest of the red cell suspension centrifugated at low speed



for five minutes and the cells washed three times and then tested for hypotonic fragility by the method of Daland and Worthley<sup>6</sup>. There was no definite increase in hypotonic fragility (hemolysis, 0.46 to 0.12 per cent) with this method over that of control (0.42 to 0.22 per cent). The method was, however, open to question because the agglutinated red cells were discarded.

In another experiment, the fragility test with hypotonic solutions showed hemolysis of normal unsensitized guinea pig erythrocytes to begin at 0.44 and end at 0.28 per cent. Erythrocytes sensitized by silicic acid (5 cc of a 10 per cent suspension of guinea pig red

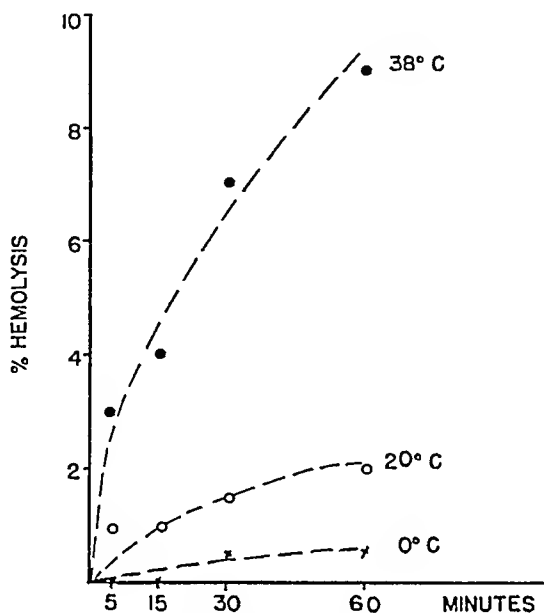


Fig 3—Rate of hemolysis with colloidal silicic acid 1:5 with added complement. Temperature is a factor in the degree of hemolysis in a colloidal silicic acid-complement system. The greatest hemolysis occurs at incubator temperature and very little at refrigerator temperature. This indicates that the reaction is to some extent a metabolic one.

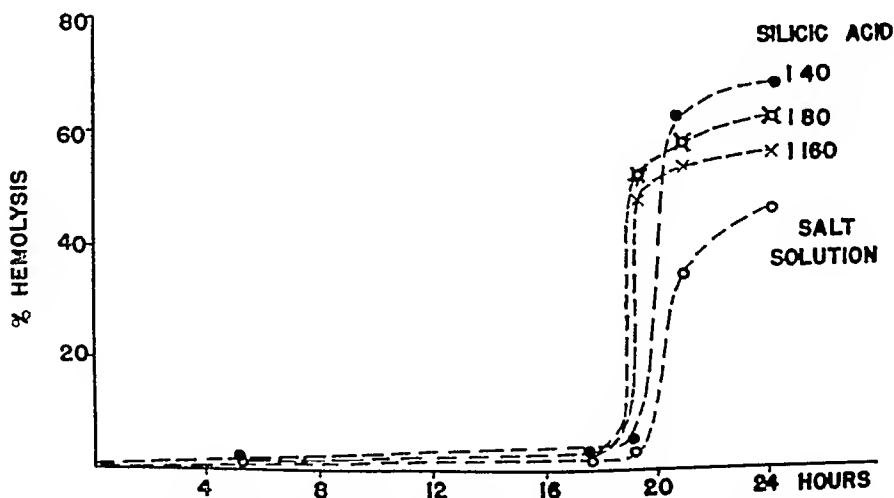


Fig 4—Hemolysis with colloidal silicic acid in various concentrations, stasis at 38° C. Erythrocytes of red cells agglutinated by silicic acid failed to result in hemolysis for eighteen hours, at the end of that time, a sharp increase in hemolysis took place, greatest with the cells agglutinated by the highest (1:40) concentration of silicic acid. It should be noted, however, that the normal control red cells also became moderately hemolyzed after twenty hours' incubation.

<sup>6</sup> Daland, G. A., and Worthley, K. The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, *J. Lab. & Clin. Med.* 20:1122, 1935.

cells, 5 cc of 1:10 silicic acid and 15 cc of physiologic solution of sodium chloride) were allowed to settle in large Evelyn tubes. The supernatant fluid was then drawn off and fresh saline solution added three times and drawn off from the sedimented red cells. After the last withdrawal, 1 drop of sedimented red cells was added to each of various concentrations of hypotonic solution of sodium chloride. By this method hemolysis began at 0.68 and ended at 0.20 per cent, a definite change. In a similar experiment, the hypotonic fragility became modified, hemolysis occurring at first between 0.44 and 0.16 and then between 0.60 and 0.16 per cent.

**Effect of Mechanical Trauma (Shaking)** Different concentrations of silicic acid were mixed with standard suspensions of guinea pig red cells and physiologic solution of sodium chloride in Hinton tubes. Six glass beads (approximately 3 mm in diameter) were added

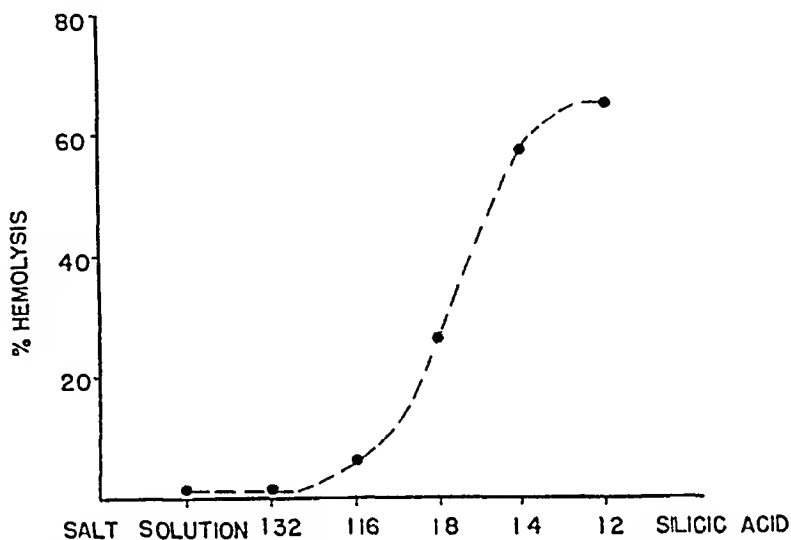


Fig 5—Hemolysis with colloidal silicic acid, mechanical fragility (shaking three hours), use of various concentrations. The degree of hemolysis of red cells treated with colloidal silicic acid and then shaken with glass beads varied directly with the concentration of silicic acid used.

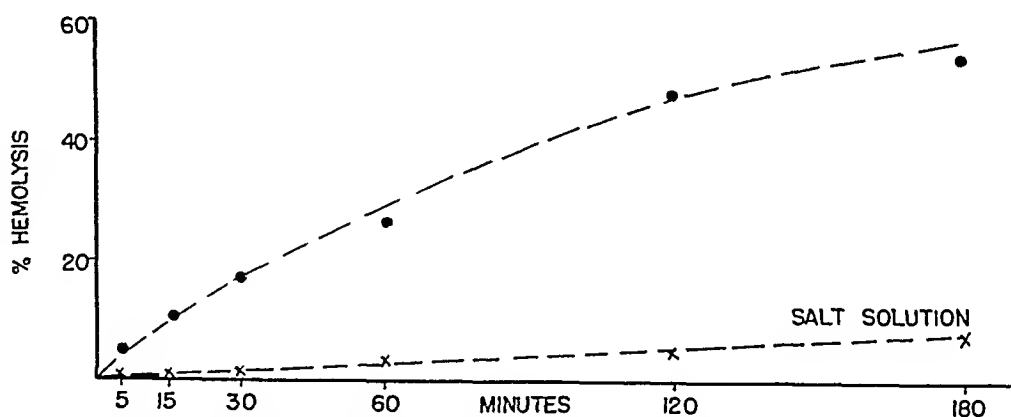


Fig 6—Hemolysis with colloidal silicic acid 1:10, mechanical fragility (shaking three hours). Red cells acted on by silicic acid without complement were readily hemolyzed by mechanical trauma (shaking with glass beads), normal red cells being only slightly affected.

to each tube, and the tubes were placed on a mechanical pipet shaker and shaken for three hours. At the end of this time, the tubes were centrifuged at low speed for three minutes, and 3 cc of the supernatant fluid was removed and added to 17 cc of a 0.1 per cent solution of sodium carbonate. The degree of hemolysis was read as hemoglobin with the Cenco photoelectric colorimeter. There was marked hemolysis with the highest concentrations of silicic acid (fig 5). The degree of hemolysis varied directly with the time of shaking, most taking place in the first fifteen minutes (fig 6). When the red cells were incubated at 37 C for one hour after "sensitization" and then shaken for one hour, there was a slight increase in the degree of hemolysis, but when red cells were first

allowed to stand for one and one-half hours at refrigerator temperature, a definite decrease in hemolysis with shaking took place (fig 7)

**Animal Experiments** Undiluted silicic acid was injected intraperitoneally daily into a guinea pig and frequent observations made of the hemoglobin, red blood cell count, white blood cell count, blood smears and hypotonic fragility. No essential changes in the values occurred during the period of injections (Dec 4-11, 1941), although doses of 3 cc each were given on the last two days.

Increasing doses (0.5 to 4 cc) of undiluted silicic acid were injected intravenously for five days into a rabbit without change in values for hemoglobin, red blood cell count or hypotonic fragility. Moderate leukocytosis (up to 34,500 leukocytes per cubic millimeter) developed.

In view of these negative results, further *in vivo* experiments were considered inadvisable.

Silicic acid, like tannic acid and other inorganic substances studied by Landsteiner and Jagic,<sup>7</sup> Landsteiner and Rock,<sup>8</sup> Reiner and Fischer<sup>9</sup> and Ponder,<sup>5</sup> exhibits unusually interesting results in relation to complement activity. Without complement there is marked agglutination of red cell suspensions, with complement hemolysis rapidly occurs. Like immune hemolytic serum, this substance may thus be called a complex hemolysin, and its interesting activities together with their significance are discussed in the next part of the paper.

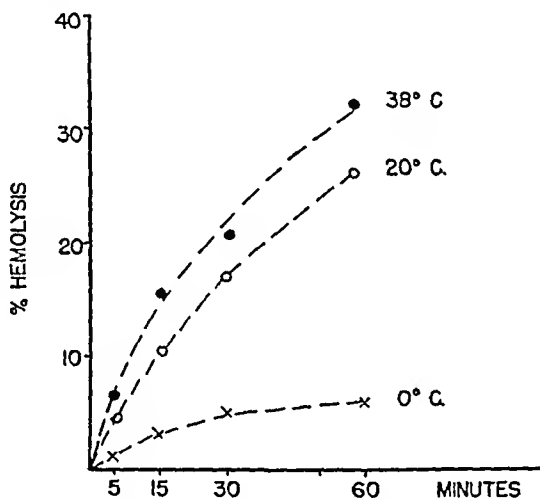


Fig 7—Hemolysis with colloidal silicic acid 1:10, stasis at various temperatures for one hour before shaking. That the degree of hemolysis with shaking was to some extent associated with metabolic changes in the red cells is evident from the fact that stasis for one hour at incubator temperature prior to shaking increased the mechanical fragility, whereas keeping the red cells at refrigerator temperature diminished the mechanical fragility.

**3 Immune Hemolytic Serum, a Complex Hemolysin**—Immune heterohemolytic serum was prepared, as in previous experiments,<sup>2</sup> by injecting guinea pig erythrocytes intravenously into rabbits and after appropriate intervals removing blood from the rabbits. The serum thus obtained possessed both agglutinative and hemolytic activities against normal guinea pig red cells *in vitro* and when the dose was varied produced hemolytic anemia of varying degrees when injected *in vivo*. In the *in vitro* experiments, a serum with a hemolytic titer of 1:64 was routinely used together with 5 or 10 per cent suspensions of guinea pig erythrocytes and fresh guinea pig complement, usually in 10 per cent dilution.

<sup>7</sup> Landsteiner, K., and Jagic, N. Ueber die Verbindungen und die Entstehung von Immunkörpern, München med Wchnschr 50 764, 1903.

<sup>8</sup> Landsteiner, K., and Rock, H. Untersuchungen über Komplementwirkung. Hämolyse durch Kieselsäure und Komplement, Ztschr f Immunitätsforsch u exper Therap 14 14, 1912.

<sup>9</sup> Reiner, L., and Fischer, O. Beiträge zum Mechanismus der Immunkörperwirkung. Ztschr f Immunitätsforsch u exper Therap 61 317, 1929.

**General Results** Immune hemolytic serum, "inactivated" by heating for one hour at 56 C, caused agglutination of guinea pig erythrocytes in high titer but no hemolysis. With guinea pig complement present, there was complete hemolysis with the serum used to a titer of 1:64 after one hour's incubation at 37 C. Doubling the amount of complement, considerably increased the hemolytic titer. Thus, complement was the actual hemolyzing agent, although it could not act on already fully agglutinated red cells.

The rate of hemolysis in the complete hemolytic system was in some measure dependent on the temperature. The most marked degrees of hemolysis took place at incubator temperature and the least at refrigerator levels (fig. 8).

**Effects of Stasis on Sensitized (Agglutinated) Red Cells (Without Complement)** Inactivated immune serum (without added complement) with a titer of 1:64 was diluted to various concentrations (1:128, 1:256 and 1:512) and mixed with 10 per cent guinea pig erythrocytes and physiologic solution of sodium chloride. The tubes were inverted once and placed in the incubator at 38 C for periods varying from five and one-half to eighty-nine hours. At the sixteen and nineteen hour periods the control tubes showed more marked hemolysis than those containing immune serum. In another experiment of this type, with somewhat different concentrations of immune serum (1:25, 1:50, 1:100 and 1:200) there was definitely more hemolysis in the control red cells than in those which were sensitized (agglutinated). Cells treated with 1:400, 1:800 and 1:1,600 dilutions of serum behaved like normal erythrocytes in one experiment but showed distinctly less hemolysis than the controls

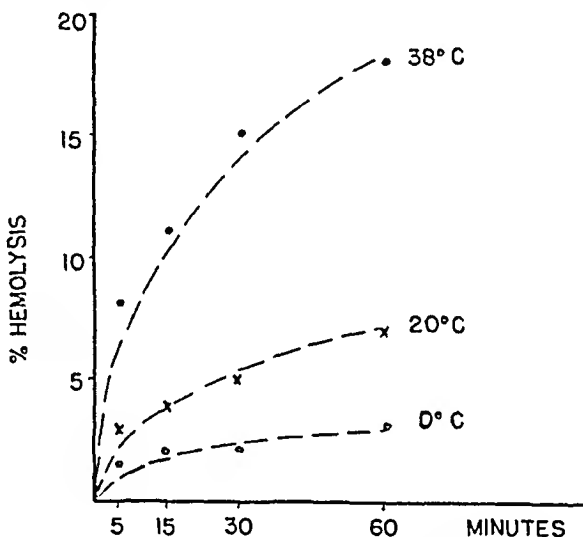


Fig. 8—Rate of hemolysis with immune hemolytic serum 1:25 with added complement. Immune hemolytic serum, like silicic acid, results in agglutination without complement; complement is the actual hemolyzing agent; the activity of complement is greatest at incubator temperature and minimal at refrigerator temperature.

in an experiment with incubation at 24 C (fig. 9). Thus, in all these experiments, the cells which were sensitized by immune serum appeared to be less liable to hemolysis by stasis than normal cells. This finding differed somewhat from the results of similar experiments with silicic acid (already described) and was thought to be due to the greater degree of agglutination (often in one solid button) by immune serum. To avoid this, very dilute concentrations of immune serum were used again, but with similar results.

**Effects on Hypotonic Fragility** Experiments to show the effect of immune serum on the hypotonic fragility of erythrocytes were for the most part unsatisfactory. If guinea pig complement was used, even the slight degree of hemolysis present at high dilutions of serum was usually sufficient to cause difficulty in reading the results. If complement was not added, marked agglutination took place; the agglutinated masses of red cells could then be either discarded or tested. If discarded, they might represent the injured red cells; if tested, their agglutination in masses might be a deterrent to the action of hypotonic solution of sodium chloride. Various methods were utilized in the attempt to avoid these difficulties, but only the last one used was moderately conclusive.

In this method, 5 cc of a 1:100 dilution of immune serum was mixed with 5 cc of a 10 per cent suspension of guinea pig red cells, 5 cc of 1:10 guinea pig complement and 10 cc of physiologic solution of sodium chloride; the cells were allowed to settle and were washed three times (not centrifuged), and the hypotonic fragility was determined in the

usual manner. With this method hemolysis of the sensitized red cells began at 0.60 per cent sodium chloride and was incomplete at 0.04 per cent. Hemolysis of the normal red cells in this experiment began at 0.44 and ended at 0.24 per cent, that of red cells allowed to stand at room temperature for eight hours and then overnight in the refrigerator at 0.46 and 0.22 per cent, that of cells incubated for one hour at 37 C., at 0.48 and 0.20 per cent, and that of cells sensitized (agglutinated) by immune inactivated serum without added complement, at 0.48 and 0.04 per cent.

Although this method offered certain advantages over that in which the cells—during the triple washing process—were centrifuged three times and although the hypotonic fragility was unquestionably increased, no definite conclusions could be drawn because of the possibility that the presence of complement resulted in some hemolysis. However, no trace of hemolysis

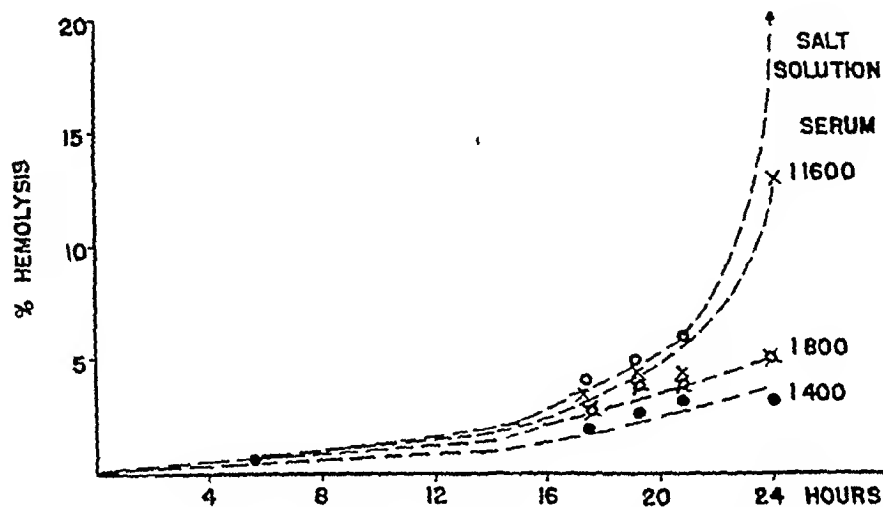


Fig 9—Hemolysis with immune hemolytic serum in various concentrations, stasis at 38 C. Stasis of red cells agglutinated by immune hemolytic serum without added complement resulted in distinctly less hemolysis than that of control red cells.

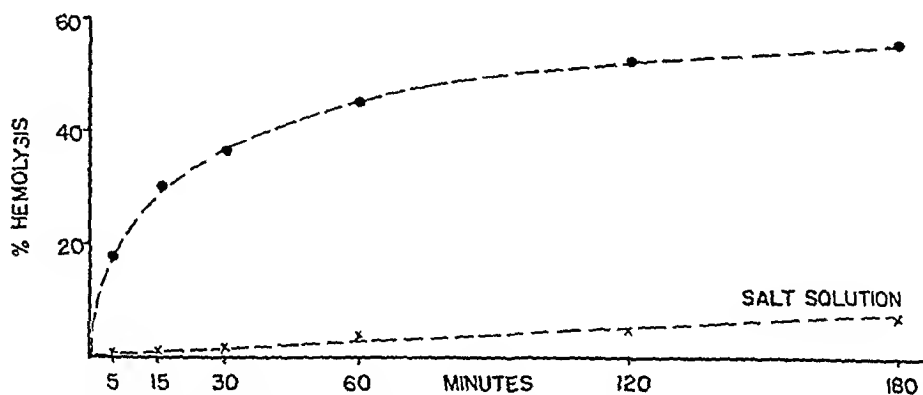


Fig 10—Hemolysis with immune hemolytic serum 1:4, mechanical fragility (shaking three hours). Red cells acted on by immune hemolytic serum when shaken with glass beads were to a large extent hemolyzed, the greatest hemolysis taking place in the first thirty minutes of shaking. Control red cells were only slightly affected by this form of mechanical trauma. As with silicic acid (fig 5), the degree of hemolysis varied directly with the concentration (titer) of serum used.

was present in the tubes holding concentrations of sodium chloride from 0.80 to 0.64 per cent, inclusive, although definite hemolysis was present in the lower concentrations.

**Effects on Mechanical Fragility.** Numerous experiments performed on the mechanical fragility of erythrocytes sensitized by immune serum demonstrated a uniformly marked hemolytic effect. The experiments were usually performed by mixing 1 cc of a dilution of inactivated immune serum with 1 cc of a 10 per cent suspension of guinea pig red cells and 3 cc of physiologic solution of sodium chloride in Hinton tubes, as previously described.

The degree of hemolysis with mechanical trauma varied directly with the concentration of immune serum and with the time of shaking (fig 10). In one experiment 55 per cent of the total hemolysis induced by three hours' shaking took place in the first fifteen minutes. The degree of hemolysis induced by shaking, with the use of very dilute serums, could be considerably enhanced by incubating the mixture of immune serum, red cells and saline solution for one hour at 37 C before shaking it.

Spherocytes, produced by injecting immune hemolytic serum into guinea pigs, when shaken for three to six hours showed no difference in mechanical fragility as compared with control red cells, although their hypotonic fragility was greatly altered. In an experiment of this type, acute hemolytic anemia (hemoglobin 9.7 Gm, red blood cells 3,670,000) was produced in a guinea pig by injection of hemolytic serum. There was spherocytosis, and hemolysis began at 0.72 and ended at 0.16 per cent sodium chloride. A 10 per cent suspension of cells from this guinea pig was shaken for three hours and compared with red cells from a guinea pig with a hemoglobin content of 14.5 Gm, a red cell count of 6,110,000 and hemolysis between 0.40 and 0.24 per cent sodium chloride. At the end of three hours of shaking, the degree of hemolysis was the same in both tubes, 3 per cent.

**Effects on Morphologic Appearance of Red Cells.** Various dilutions of serum with and without complement were mixed with guinea pig red cells and incubated at 38 C for one hour (1 cc of serum dilution, 1 cc of 10 per cent guinea pig complement, 1 cc of a 10 per cent suspension of guinea pig red cells and 2 cc of physiologic solution of sodium chloride). At the end of the hour, the tubes were inverted once for mixing and a drop of each dilution was placed on a slide and examined under a cover slip with high magnification dry and oil immersion lenses. With the higher concentrations (1:30 and 1:60) of serum without complement, there was agglutination with "thorn apple deformity" (fig 11A), in the presence of complement, no thorn apple forms were present, but there were definite spherocytosis and poor rouleau formation with thickened red cells (fig 11B). Control red cells showed crenation, which could readily be discriminated from thorn apple deformity, and either questionable spherocytosis or no spherocytosis.

**Animal Experiments.** These have already been described.<sup>2</sup> The injection into guinea pigs of large doses (0.5 to 1 cc) of immune hemolytic serum intraperitoneally was followed by a fulminating hemolytic anemia characterized by extreme spherocytosis, increased hypotonic fragility, hemoglobinuria and quick death. Moderate doses given intraperitoneally daily resulted in acute hemolytic anemia, and small doses (0.1 cc) given daily produced a subacute type of anemia with moderate spherocytosis, marked reticulocytosis, "pseudomacrocytosis" and only a slight change in hypotonic fragility.

Immune hemolytic serum, like silicic acid, is a complex hemolysin. The greatest effects on hemolysis in vitro, as with silicic acid, were obtained with either mechanical trauma or complement activity. Although erythrostasis for short periods might be important in enhancing the effects of both complement activity and mechanical trauma, stasis alone appeared to have little effect on sensitized (agglutinated) red cells. Thus, although the hypotonic fragility of red cells acted on by immune body might not be significantly altered, some change in the colloidal nature of the erythrocyte and/or its envelope appeared likely, since it became readily hemolyzed (a) by complement and (b) by mechanical injury.

**4 Concanavalin A, a Pure Agglutinin.**—Ham and Castle used concanavalin A, a crystalline protein (globulin) derived from the jack bean,<sup>10</sup> to produce agglutination of red cells in vitro and hemolytic anemia, presumably by agglutination effects, in the experimental animal. We obtained some of this material from J. B. Sumner in 96 per cent concentration dissolved in a saturated solution of sodium chloride.

For experimental use, 0.1 cc (containing 9.6 mg) of the saturated solution was diluted to isotonicity by the addition of 4.1 cc of physiologic solution of sodium chloride. Dilutions of the isotonic solution with further amounts of the saline solution were labeled 1:10, etc. Experiments with guinea pig red cells, complement, stasis and mechanical fragility were carried out by the same technique as with silicic acid and immune hemolytic serum.

**General Results.** Concanavalin A is an extremely potent agglutinin of the erythrocytes of the guinea pig, of the rabbit and of the dog but not of the human being. In isotonic solution of sodium chloride, i. e. in a concentration of 230 mg per hundred cubic centimeters,

<sup>10</sup> Sumner, J. B., and Howell, S. F. The Identification of the Hemagglutinin of the Jack Bean with Concanavalin A, *J. Bact.* **32** 227, 1936.

it caused extreme agglutination of 10 per cent suspension of guinea pig red cells in all dilutions up to approximately 1 10,000. The addition of guinea pig complement in different amounts to the various concentrations failed to cause any trace of hemolysis. Incubation with complement for one hour at 38 C also failed to cause hemolysis. Thus, concanavalin A is a pure agglutinin, differing from the agglutinins silicic acid and immune serum which not only result in agglutination but facilitate hemolysis by complement.

**The Effects of Stasis** Different concentrations (1 10 to 1 100,000) of isotonic solution of concanavalin A in 1 cc amounts were mixed with 1 cc of 10 per cent suspension of guinea pig red cells and 3 cc of physiologic solution of sodium chloride in Hinton tubes and allowed to stand for periods varying from three to twenty-four hours in a water bath

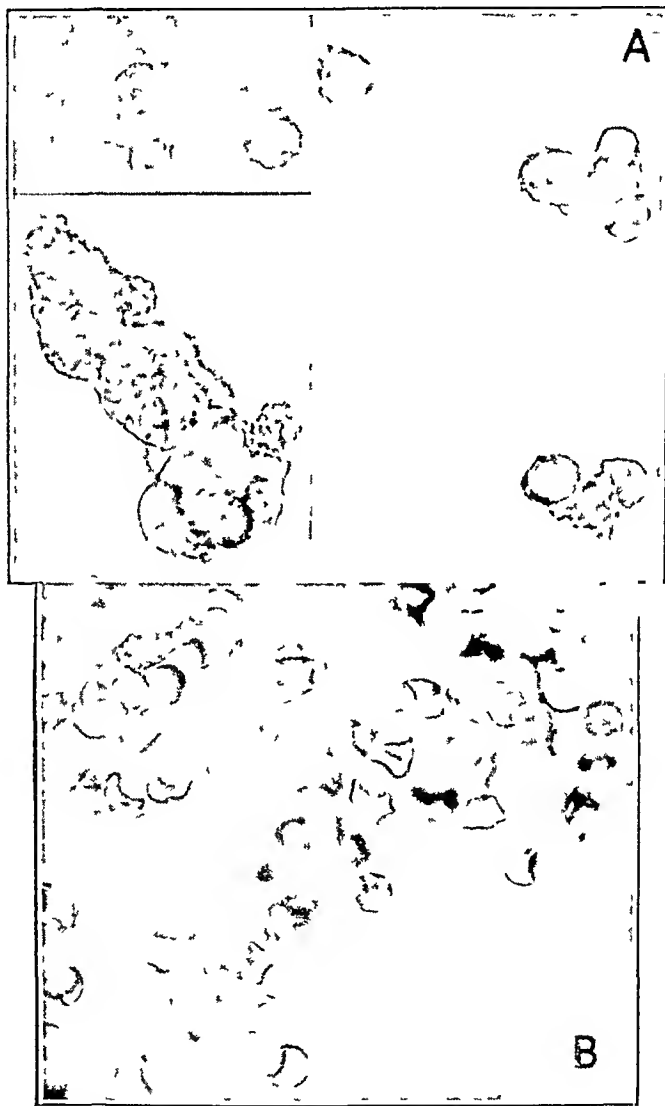


Fig 11—Red cells in contact with hemolytic serum from rabbits inoculated with guinea pig red blood cells. *A*, without added complement. Note the agglutination phenomena and the thorn apple appearance of the red blood cells. *B*, with added complement. Many of the red cells are almost completely hemolyzed. There is little thorn apple appearance. The red cells tend to be spherocytic and to form bizarre rouleaux.

at 37 C. The degree of hemolysis varied from experiment to experiment directly with the concentration used and the time of stasis. The greatest degrees of hemolysis were present with the highest concentrations of concanavalin A and the longest periods of incubation. When care was taken to avoid agglutination on the sides of the tubes by transferring the agglutinated red cells to other tubes, the degree of hemolysis was distinctly less than when this precaution was not observed, in fact, in one such experiment, there appeared to be actual inhibition of hemolysis (fig 12).

The greatest degrees of hemolysis, as with silicic acid and immune hemolytic serum, were present at incubator temperature, keeping the agglutinated cells at ice box temperature effectively inhibited the hemolytic tendency, at room temperature, various degrees of hemolysis took place

The results with stasis thus varied from experiment to experiment and appeared to depend to some degree on the extent of agglutination on the sides of the tubes and on the reaction of the agglutinated cells with the water of condensation. It was therefore impossible to draw any definite conclusion regarding the effect of erythrosthesis on the agglutinated red cells.

**The Effects on Hypotonic Fragility** Cells agglutinated by concanavalin A in various concentrations of distilled water to which was added hypotonic solution of sodium chloride failed to be hemolyzed, which shows that such cells are unusually resistant. However, in experiments in which the same technic was used as that employed with immune hemolytic serum, in which the agglutinated red cells were allowed slowly to settle and were washed three times (without centrifugation), there was a definite although slight increase in hypotonic fragility (hemolysis, between 0.38 and 0.20 to between 0.52 and 0.04 per cent), indicating again—as with silicic acid and immune hemolytic serum—that the process of agglutination effected some injury to the envelope of the erythrocyte and an increase in sphericity of the cell itself.

**The Effects of Mechanical Trauma** The most marked and most consistent results were obtained with the trauma obtained by shaking the red cells with glass beads. The same

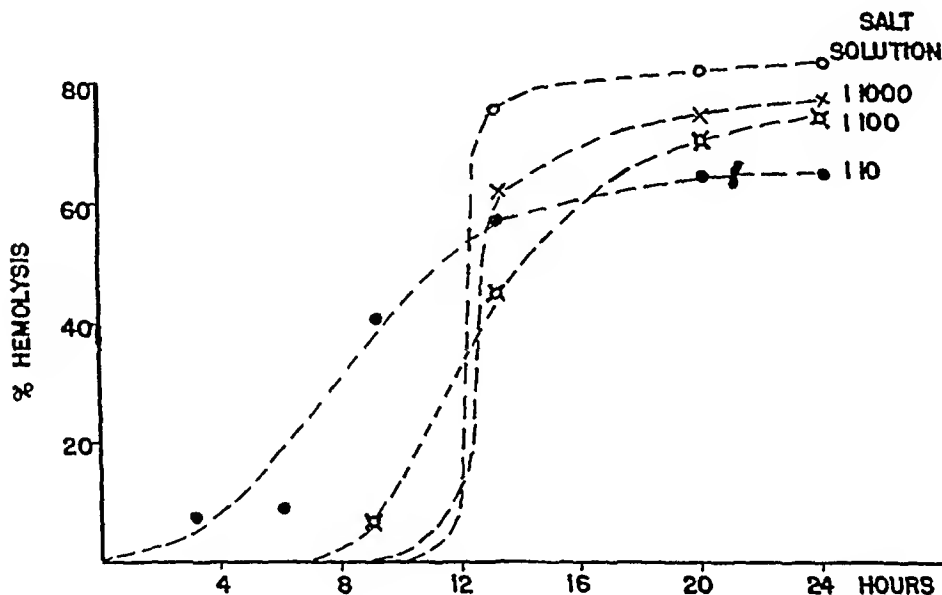


Fig 12—Hemolysis with concanavalin A in various concentrations, stasis at 38 C. Concanavalin A, a pure agglutinin, results only in agglutination even with added complement. Stasis of red cells agglutinated by concanavalin A resulted in a certain degree of hemolysis occurring prior to that of normal red cells, at twelve hours and thereafter, however, there was more hemolysis of the control red cells than of those affected by concanavalin A.

technic was utilized as with silicic acid and immune serum. As with these substances, the most marked hemolysis took place with the highest concentration of concanavalin A (1:10) and with the most shaking (fig 13). However, by far the greatest amount of hemolysis (approximately 50 per cent of the total) took place within the first fifteen minutes of shaking. Somewhat more hemolysis took place if the agglutinated red cells were allowed to incubate for one hour prior to being shaken.

**Animal Experiments** Guinea pigs inoculated intraperitoneally with undiluted and diluted concanavalin A died with marked abdominal distention and without the development of hemolytic anemia or spherocytosis. On the other hand, as Castle and Ham have already shown, in rabbits inoculated intravenously with concanavalin A acute hemolytic anemia developed, with spherocytosis and increased hypotonic fragility. This indicated that a pure agglutinin could produce hemolytic anemia only when intravascular agglutination could be produced.

Concanavalin A, a pure agglutinin, unlike the complex agglutinin hemolysins silicic acid and immune hemolytic serum, produces only agglutination, complement is without further effect. However, like the more complex substances studied, it



produces definite alterations of the envelope of the red cell. This is demonstrated by a slight alteration in hypotonic fragility and a marked alteration in the mechanical fragility, the reaction to erythrostatics being equivocal. When injected directly into the circulation, concanavalin A caused spherocytosis and hemolytic anemia, presumably as the result of intravascular agglutination.

#### COMMENT

The experiments described demonstrate that hemolysis of the red cell may be accomplished by pure or simple hemolysins (such as saponin), by complex hemolysins or agglutinins (silicic acid and immune hemolytic serum) and by pure agglutinins (such as concanavalin A). Saponin hemolyzes the red cell directly without the mediation of other factors, but the complex hemolysins and the agglutinins may require for hemolysis such primary factors as complement activity and mechanical trauma and such secondary factors as erythrostatics and a suitable temperature (table 1). It is possible that other factors may also be involved in certain conditions, namely the  $p_H$ , the concentrations of such electrolytes as sodium

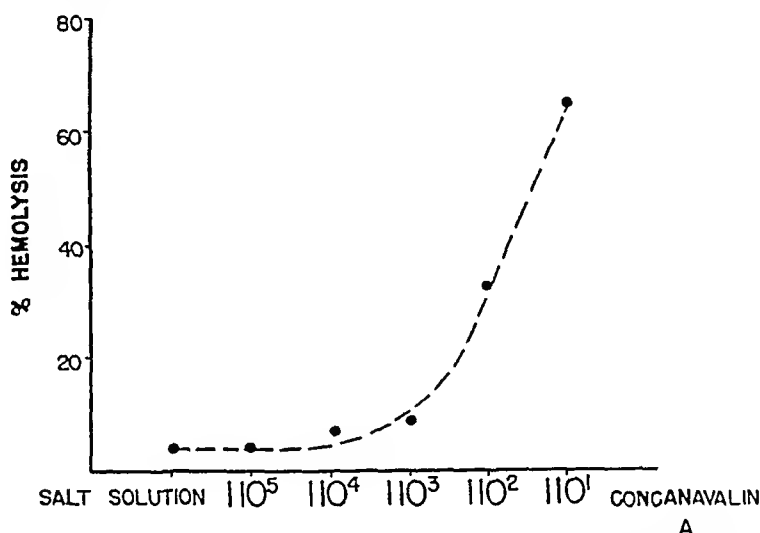


Fig 13—Hemolysis with concanavalin A and mechanical fragility (shaking three hours), showing the effect of various concentrations. Red cells agglutinated by concanavalin A were readily hemolyzed by the mechanical trauma of shaking with glass beads for three hours, the degree of hemolysis was dependent to a large extent on the concentration of concanavalin A used.

and potassium, the degree of glycolysis, certain physical factors and certain splenic activities other than those of stasis.

Our experiments indicated that silicic acid, immune hemolytic serum and concanavalin A all produced injury to the red cell, which could be demonstrated in various ways. When sensitized (agglutinated) by these substances the red cell became vulnerable to mechanical trauma, and with the first two substances to complement activity. A slight though definite increase in hypotonic fragility also became evident. In all the experiments, certain metabolic activities were apparent, as indicated by the definitely inhibitory effect of low temperatures and the greatly enhancing effect of incubator temperatures. In these *in vitro* experiments, erythrostatics of agglutinated red cells appeared to be of secondary importance as compared with the factors of mechanical trauma and complement activity. The nature of the injury to the erythrocyte produced by the various substances was studied by Reiner and Fischer,<sup>9</sup> who concluded that dehydration of the surface envelope

of the erythrocyte takes place, with the resultant changes in its colloidal structure. The thorn apple deformity seen by direct inspection is probably evidence of this.

The methods used for testing injury to the red cells in vitro probably have their counterparts in the pathologic processes of experimental and clinical hemolytic states. Thus, red cells sensitized by immune hemolysin and presumably first agglutinated become hemolyzed either by the mechanical trauma of passage through the circulation or by complement, a normal constituent of blood. It is probable that these two factors act together and are to some extent aided by stasis since in our in vitro experiments stasis for a short time just prior to mechanical trauma appeared to enhance the effects of shaking. Red cells sensitized by a simple agglutinin, such as concanavalin A, may become hemolyzed in vivo owing to the combined activity of the factors of stasis and mechanical trauma.

Ham and Castle<sup>3</sup> have recently stressed erythrosthesis as the basic factor underlying many, if not all, the hemolytic processes, both of experimental and of clinical origin. Chiefly on the basis of Knisely's work<sup>11</sup> they concluded that the normal spleen has two main functions, which are reproducible in the test tube.

TABLE 1—*Hemolytic Mechanisms*

Simple (pure) hemolysin → Red blood cells → Hemolysis (complete)		
or		
Incomplete hemolysis (spherocytosis)		
Complex hemolysin	} → Red blood cells →	Agglutination (change in surface envelope)
Immune hemolysin		
		{ Complement activity } { Mechanical trauma with and without stasis }
		→ Hemolysis
		(a) Complete
		(b) Incomplete (spherocytosis)
		↓
		Stasis (spleen, etc.)
		↓
		Hemolysis complete
Agglutinin → Red blood cells → "Sensitization"		
↓		
Increased mechanical fragility		
↓		
Hemolysis or Incomplete hemolysis		
Physical Agents → Red blood cells → Hemolysis, complete or incomplete		
Heat		
Cold		
Mechanical trauma, etc		

erythrosthesis and erythroconcentration. They stated that unusual erythrosthesis in the presence of normal red cells, which they conceived of as occurring in heart failure, "hypersplenic" anemia, favism, certain agglutination reactions, increased blood viscosity or the tendency to rouleau formation, is the cause of hemolytic anemia. The experimental hemolytic anemia which they produced by concanavalin A was interpreted as due to the extreme erythrosthesis induced by the agglutinating effect of the chemical. The experimental hemolytic anemia of immune hemolytic serum, which Dameshek and Schwartz<sup>2</sup> stated was due to hemolysin activity, was interpreted by Ham and Castle as due to the action of the agglutinins present, with resultant "erythrosthesis."

These conclusions are in several respects at variance with ours. There is in the first place very little evidence that unusual erythrosthesis occurs in the various conditions listed. Furthermore, although the spleen is doubtless an organ of erythrosthesis, it probably has other than purely "test tube" functions. Many of

11 Knisely, M. H. Spleen Studies. I. Microscopic Observations of the Circulating System of Living Unstimulated Mammalian Spleens, *Anat. Rec.* **65** 23, 1936, II. Microscopic Observations of the Circulating System of Living Traumatized Spleens and of Dying Spleens, *ibid.* **65** 131, 1936.

its cells belong to the highly phagocytic reticuloendothelial system. According to Bergenhem and Fåhræus,<sup>12</sup> the spleen contains in greatest concentration the physiologic lysin called lysolecithin, which may alter the thickness of the red cells. Other functions, such as the hormonal, have been listed by Singer, Miller and Dameshek.<sup>13</sup>

Regarding that group of hemolytic diseases in which spherocytosis is present and in which the hemolysis is said to be due to the effects of normal erythro-stasis on abnormal red cells, Ham and Castle made no attempt to explain the reason for the presence of spherocytosis, even though in some cases a definite cause is present (sulfonamide drugs, arsine [ $\text{AsH}_3$ ], etc.). It has been our contention that when a hemolytic substance produces incomplete hemolysis, spherocytosis results. The spherocyte may thus be said to be an indicator of hemolytic activity and appears after injury to the red cell by hypotonic solution of sodium chloride, saponin, lecithin, lysolecithin, immune hemolytic serum and even by such purely physical means as heat<sup>13a</sup> and mechanical trauma. According to this conception, the presence of spherocytosis in cases of hemolytic anemia, whether congenital or acquired, indicates not an abnormality in formation of the red cells but rather the presence of some sort of hemolytic agent—immunologic, chemical or physical—even though a hemolysin as such can only occasionally be demonstrated.

Our experiments with immune hemolytic serum in which various degrees of spherocytosis, increased hypotonic fragility and hemolytic anemia were produced seemed adequately explained on the basis of the hemolysin content of the serum. The actual hemolytic mechanism is, however, probably more complex than that of simple lysis. As pointed out previously, immune hemolytic serum, which is ordinarily considered to be simply a hemolysin, is in reality a complex material containing among other substances amboceptor, or sensitizer, which brings about agglutination and thus definite injury to the red cell. Attempts to differentiate clearly and to separate agglutinin from hemolysin have been for the most part unsuccessful, and for this and other reasons some immunologists have a "unitarian" concept of agglutination and hemolysis. Numerous experiments<sup>13b</sup> dating from the time of Bordet have shown that amboceptor differs from complement, which is the actual hemolyzing substance and which can act only on the already injured erythrocyte. In anemia due to concanavalin A, the mechanical trauma involved in the circulation of agglutinated masses of red cells may be of at least as much importance from the hemolytic standpoint as the factor of stasis. Thus our conception of hemolysis as an active process differs from that of Ham and Castle, who stress the more passive process of erythro-stasis.

12 Bergenhem, B, and Fåhræus, R. Ueber spontane Hamolysinsbildung im Blut unter besonderer Berücksichtigung der Physiologie der Milz, *Ztschr f d ges exper Med* **97** 555, 1936.

13 Singer, K, Miller, E, and Dameshek, W. Hematological Changes Following Splenectomy in the Human with Particular Reference to Target Cells, Hemolytic Index, and Lysolecithin, *Am J M Sc* **202** 171, 1941.

13a Isaacs, R, Brock, B, and Minot, G R. Resistance of Immature Erythrocytes to Heat, *J Clin Investigation* **1** 425, 1925. Ham, T H, and Chew, S C. Studies on Destruction of Red Blood Cells. III. Mechanism of Hemoglobinuria in Thermal Burns. Spherocytosis and Increased Osmotic Fragility of Erythrocytes, to be published.

13b Lieberman, L V, and Fenyvessy, B V. Ueber Serumhamolyse, *Jahresb f Immunitätsforsch u exper Therap* **7** 2, 1910. Ehrlich, P. Experimentelle Untersuchungen über Immunität. I über Ricin, *Deutsche med Wchnschr* **17** 976, 1891. von Baumgarten, P. Die Osmologische Auffassung der Hamo- und Bakteriolyse, *Biochem Ztschr* **11** 21 1908.

From the clinical standpoint, certain considerations are in order. Unusual erythrostatics without the presence of agglutinins (as in heart failure) has been stated to produce increased hypotonic fragility and hemolysis<sup>14</sup>. However, the increase in fragility is minimal, and the observed increase in fecal urobilinogen output is based not necessarily on erythrostatics but simply on an increased removal of red cells from the body. In polycythemia vera, in which erythrostatics, viscosity, decreased blood flow, etc., are maximal, there is no evidence of an increased hemolytic tendency, in fact, quite the reverse occurs<sup>14a</sup>. In multiple myeloma, in which the blood globulins are greatly increased, with resultant marked rouleau formation and actual pseudoagglutination, there is rarely any evidence of even a slight increase in hemolysis. In experiments on dogs with splenic vein thrombosis,<sup>15</sup> partial or complete, in which marked splenic stasis was present, there was no evidence of spherocytosis or increased hypotonic fragility. In fact, the red cells tended to become thinner (target cells) and more resistant to hypotonic solutions. In sickle cell anemia, Cooley's erythroblastic anemia, target cell anemia<sup>16</sup> and various types of Mediterranean anemia, there is usually increased hemolysis and yet the red cells are unusually resistant to hypotonic solutions of sodium chloride. All of these considerations tend to refute the conceptions of Ham and Castle regarding the importance of erythrostatics and agglutination in the development of increased hemolysis.

From the positive standpoint, furthermore, in certain cases acute hemolytic anemia is associated with the presence of hemolysins in the serum,<sup>17</sup> in paroxysmal (cold) hemoglobinuria an autohemolysin is present which appears to act directly on the red cells. Neither paroxysmal nocturnal hemoglobinuria<sup>18</sup> nor march hemoglobinuria<sup>19</sup> has been found to be concerned with the factors of agglutination or erythrostatics. The former condition appears to be concerned with the presence of sensitized red cells, which in the presence of complement become hemolyzed. In march hemoglobinuria, the sudden hemolysis is brought about by severe muscular exercise rather than by stasis. In cases of "symptomatic" hemolytic anemia,<sup>4</sup> in which the increased hemolysis is associated with some more fundamental condition, such as lymphatic leukemia, Hodgkin's disease and dermoid cyst, there is no evidence of stasis. Removal of a dermoid cyst in 1 of our cases resulted in complete cessation of the hemolytic process.

As previously stated, our conception of the various types of hemolytic syndromes remains an active one and is fundamentally concerned with the activity of hemol-

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14 Waller, J. Cause of Increased Fragility of Erythrocytes in Congestive Heart Failure, *Proc Soc Exper Biol & Med* **42** 64, 1939.

14a Miller, E. B., Singer, K., and Dameshek, W. Use of the Daily Fecal Output of Urobilinogen and the Hemolytic Index in the Measurement of Hemolysis, *Arch Int Med* **70** 722 (Nov.) 1942.

15 Miller, E. B., Singer, K., and Dameshek, W. Experimental Production of Target Cells by Splenectomy and Interference with Splenic Circulation, *Proc Soc Exper Biol & Med* **49** 42 and 45, 1942.

16 Dameshek, W. "Target Cell Anemia" An Erythroblastic Type of Cooley's Erythroblastic Anemia, *Am J M Sc* **200** 445, 1940.

17 Dameshek, W., and Schwartz, S. O. Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), *Medicine* **19** 231, 1940.

18 Ham, T. H., and Dingle, J. H. Studies in Destruction of Red Blood Cells. II. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, Certain Immunological Aspects of the Hemolytic Mechanism with Special Reference to Serum-Complement, *J Clin Investigation* **18** 657, 1939.

19 Gilligan, D. R., and Blumgart, H. L. March Hemoglobinuria. Studies of the Clinical Characteristics, Blood Metabolism and Mechanism, with Observations on Three New Cases and Review of the Literature, *Medicine* **20** 341, 1941.

ysins The word hemolysin may be utilized for any substance which injures the red cell, rendering it liable to hemolysis (tables 2 and 3) Included are (a) pure or simple hemolysins (saponin, lecithin, lysolecithin, the Donath-Landsteiner hemolysin of paroxysmal cold hemoglobinuria, arsine and probably sulfanilamide, which causes changes in the hemoglobin structure of the red cell), (b) complex hemolysins (silicic acid, tannic acid, immune hemolysin and other ill defined hemolysins), and (c) agglutinins (isoagglutinins, autoagglutinins, pan-agglutinins and concanavalin A) In addition, there are probably hemolytic agents of more purely physical type—heat, cold, mechanical injury—which may directly

TABLE 2—Hemolytic Syndromes Etiologic Factors

Hemolysins	Agglutinins	Spleen	Inherited factors
Simple	Isoagglutinins	Passive (erythrostatics)	Sickle cell
Sulfanilamide	Transfusion reactions	Physical factors	Oval cell } Meditterra
Snake venom	Wrong type	Heat	Target cell } near anemia
Other chemicals, toxins	Subgroups	Cold	? Spherocyte
Complex—including	Rh factor	Mechanical injury	
immune hemolysis	Erythroblastosis	Congenital hemolytic	
Known	fœtalis	jaundice	
Acute hemolytic	Rh factor	Acquired spherocytosis	
anemia with	Autoagglutinins	Various causes	
hemolysinaemia	Acute hemolytic	Active (abnormal)	
Paroxysmal (cold)	anemia	Abnormal hemolysin	
hemoglobinuria	Sulfonamide drugs	production (hyper	
Possible	Virus pneumonia	splenism)	
Acute hemolytic		Acute hemolytic	
anemia without		anemia ?	
hemolysinaemia		Congenital hemolytic	
Congenital hemolytic		jaundice crises ?	
jaundice			
Symptomatic hemo			
lytic anemia (leuke			
mia, Hodgkin's			
disease dermoid			
cirrrosis)			
Paroxysmal nocturnal			
hemoglobinuria			

TABLE 3—Development of Hemolytic Syndromes\*

Inherited factors	→Red blood cells	→Injury to red blood cells	→	Hemolysis
Target cell				
Sickle cell	→Red blood cells	→Injury to red blood cells	→	Incomplete hemolysis (spherocytosis)
Spherocyte ?				
Hemolysins	→Red blood cells	→Injury to red blood cells	→	Incomplete hemolysis (spherocytosis)
Simple				
Complex (may be of	→Red blood cells	→Injury to red blood cells	→	Incomplete hemolysis (spherocytosis)
splenic origin)				
Agglutinins	→Red blood cells	→Injury to red blood cells	→	Incomplete hemolysis (spherocytosis)
Simple				
Complex	→Red blood cells	→Injury to red blood cells	→	Incomplete hemolysis (spherocytosis)
Physical factors				

\* Hemolytic syndromes are due to red cell injury as a result of the activity of hemolysins, agglutinins, inherited factors and certain physical agents. The injured red cells are vulnerable to such factors as erythrostatics, mechanical trauma in the circulation, the activity of complement and splenic activity. As a result, either incomplete hemolysis (spherocytosis) or complete hemolysis results.

injure the exposed red cell. Certain hemolysins may be demonstrable in the blood, certain of them are demonstrable only by the effects they produce. Thus, spherocytosis without demonstrable hemolysins, red cells abnormally fragile to mechanical trauma and red cells abnormally susceptible to an acid pH or to complement (paroxysmal nocturnal hemoglobinuria) may all indicate the effect of adsorption of hemolysin by the erythrocytes. The place of the spleen in this etiologic discussion is obscure. That it is a simple organ of erythrostatics and without other function is difficult to believe in view of the dramatic results which have attended splenectomy in certain of our cases of acquired acute anemia with or without hemolysinaemia. In such cases the spleen is evidently a primary

organ in the production of hemolysin. In many cases of hemolytic anemia, however, the spleen is perhaps of only secondary importance. In certain cases of hemolytic anemia—sickle cell anemia, Mediterranean anemia of various grades of severity (Cooley's anemia, target cell anemia)—which are associated with an increased hypotonic resistance of the erythrocytes, the mechanisms of the increased hemolysis appear to be based on hereditary factors which are at present obscure.

We believe, therefore, that hemolytic syndromes are due to many different mechanisms rather than to some one etiologic factor (action of hemolysin, erythrocytosis). Much work remains to be done in clarifying these mechanisms further and in applying knowledge of them to the clinical syndromes. In the present paper the injurious effects of pure and complex hemolysins and of agglutinin have been partially analyzed and the concept of erythrocytosis criticized.

#### SUMMARY AND CONCLUSIONS

The effects on red cells of simple lysins, complex hemolysins and agglutinins were studied in relation to such factors as stasis, temperature, mechanical trauma and complement activity. The substances used were saponin (a simple lysin), colloidal silicic acid and immune hemolytic serum (complex hemolysins) and concanavalin A (a pure agglutinin).

Simple lysins act directly on the red cells, producing either complete hemolysis or spherocytosis—incomplete hemolysis. Complex hemolysins produce sensitization (actually agglutination) by means of amboceptor and then hemolysis by means of (a) complement activity or (b) mechanical trauma. A pure agglutinin produces agglutination, hemolysis may then be produced by mechanical trauma (shaking with glass beads). The factor of erythrocytosis in our experiments seemed minimal.

We believe that hemolysis is an active process due to red cell injury by a variety of agents, such as pure hemolysins, complex hemolysins or agglutinins. Red cell injury may be measured not only by an increase in hypotonic fragility (present only with spherocytosis) but by other means, such as the mechanical fragility, the reaction to an acid  $p_H$  and the reaction to complement. Erythrocytosis, a passive phenomenon, is probably of only minor importance in the hemolytic processes. In polycythemia vera and splenic vein thrombosis, in which erythrocytosis is marked, and in multiple myeloma, with increased rouleau formation and pseudo-agglutination, increased hemolysis is not present.

We believe that spherocytosis indicates incomplete hemolysis by means of the activity of some hemolytic agent, the presence of which may or may not be readily discernible. The spherocyte is vulnerable to stasis and may become completely hemolyzed by this means. Thus, stasis may be of only secondary importance to the activities of hemolysin, agglutinin and other factors.

The place of the spleen is still obscure. We believe, however, that it is probably more than a simple organ of stasis and may have an active hemolytic function, particularly in certain cases of acquired hemolytic anemia.

Hemolytic processes are probably due to various causes, among them being the activity of hemolysins, both simple and complex, and of agglutinins, certain hereditary injuries to the red cells and certain splenic dysfunctions. It is impossible to explain hemolysis on the basis of a single factor, such as erythrocytosis (Ham and Castle) or the activity of hemolysins (Dameshek and Schwartz). If by hemolysin is meant any substance causing injury to the red cells, the latter theory seems more probable.

# CLINICAL MANIFESTATIONS OF WEIL'S DISEASE WITH PARTICULAR REFERENCE TO MENINGITIS

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DETROIT

Before 1935 only 11 cases of Weil's disease had been reported from the United States<sup>1</sup> Since that time additional cases have been reported with increasing rapidity<sup>2</sup> Several excellent summaries<sup>3</sup> of the clinical manifestations of the disease have also appeared in the American and foreign literature Nevertheless it is still not widely appreciated in America that this malady may occur in a meningitic form and that jaundice is not a necessary concomitant

## HISTORY AND INCIDENCE OF MENINGITIS IN WEIL'S DISEASE

What would appear to be the first recorded case of meningitis in Weil's disease was reported by Laubry and Parvu,<sup>4</sup> of Paris, France, in October 1910 These authors described 3 atypical cases of lymphocytic meningitis, 1 of the patients had jaundice and a clinical course which simulated that of Weil's disease One week later Gullam and Richet<sup>5</sup> described, and illustrated with 4 case reports, a distinct clinical syndrome of jaundice and meningitis, which in retrospect was probably Weil's disease It remained, however, for Costa and Troisier,<sup>6</sup> in 1916, to demonstrate that *Leptospira icterohaemorrhagiae* was responsible for the condition and that the meningeal form could occur without jaundice

As European physicians, particularly those in the Netherlands, have become more conscious of the disease and its variations, an increasing number of cases of the nonicteric and meningeal form have been reported A fair proportion of the cases without jaundice have been characterized by the meningeal syndrome

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1 Jeghers, H J, Houghton, J D, and Foley, J A Weil's Disease Report of Case with Post Mortem Observations and Review of Recent Literature, Arch Path **20** 447-476 (Sept) 1935

2 (a) Blake, F G Weil's Disease in the United States Report of a Case in Connecticut, New England J Med **223** 561-565 (Oct 10) 1940 (b) Ashe, W F, Pratt-Thomas, H R, and Kumpe, C W Weil's Disease A Complete Review of American Literature and an Abstract of the World Literature, Seven Case Reports, Medicine **20** 145-210 (May) 1941 (c) Larson, C L Weil's Disease A Report of Fifty-One Cases Occurring in Puerto Rico and the United States, Pub Health Rep **56** 1650-1655 (Aug 15) 1941

3 Walch-Sorgdrager, B Leptospiroses, Bull Health Organ, League of Nations **8** 143-386, 1939 Jeghers and others<sup>1</sup> Blake<sup>2a</sup> Ashe and others<sup>2b</sup>

4 Laubry, C, and Parvu, M Syndrome meninge avec lymphocytose rachidienne d'origine indeterminee, Bull et mem Soc med d hop de Paris **30** 236-244 (Oct 21) 1910

5 Gullam, G, and Richet, C Étude sûr une maladie infectieuse caracterisee par de l'ictere et un syndrome meningee, Bull et mem Soc med d hôp de Paris **30** 289-299 (Oct 28) 1910

6 Costa, S, and Troisier, J Reactions méningees dans la spirochetose ictero-hemorragique Virulence du liquide cephalorachiden, Bull et mem Soc med d hôp de Paris **40** 1802-1806 (Nov 10) 1916 Costa, S, and Troisier, J Meningite avec subictere dans la spirochetose icterhemorragique, ibid **40** 1928-1931 (Nov 24) 1916

Between 1924 and 1939 Walch-Sorgdrager,<sup>3</sup> of Amsterdam, confirmed the diagnosis of 327 cases by either bacteriologic or serologic means. Of these, 129 cases were without jaundice. Twenty of the nonjaundiced patients presented the clinical picture of serous meningitis. As his study progressed, the incidence of the meningeitic form increased, cases of that type comprising about one third of the cases without jaundice reported during the last two years. In about 10 per cent of the 248 cases of Weil's disease reported from Great Britain prior to 1939 there was clinical and laboratory evidence of meningitis.<sup>7</sup> In the American literature cases of Weil's disease with meningitis and jaundice have been reported by Goldberg and Davens<sup>8</sup> and Bloom and Walker.<sup>9</sup>

Within the past year and a half we have observed 13 cases of Weil's disease which reemphasized the frequency of meningeal involvement in this malady. In 2 of these cases there was both clinical and laboratory evidence of meningitis, in 7

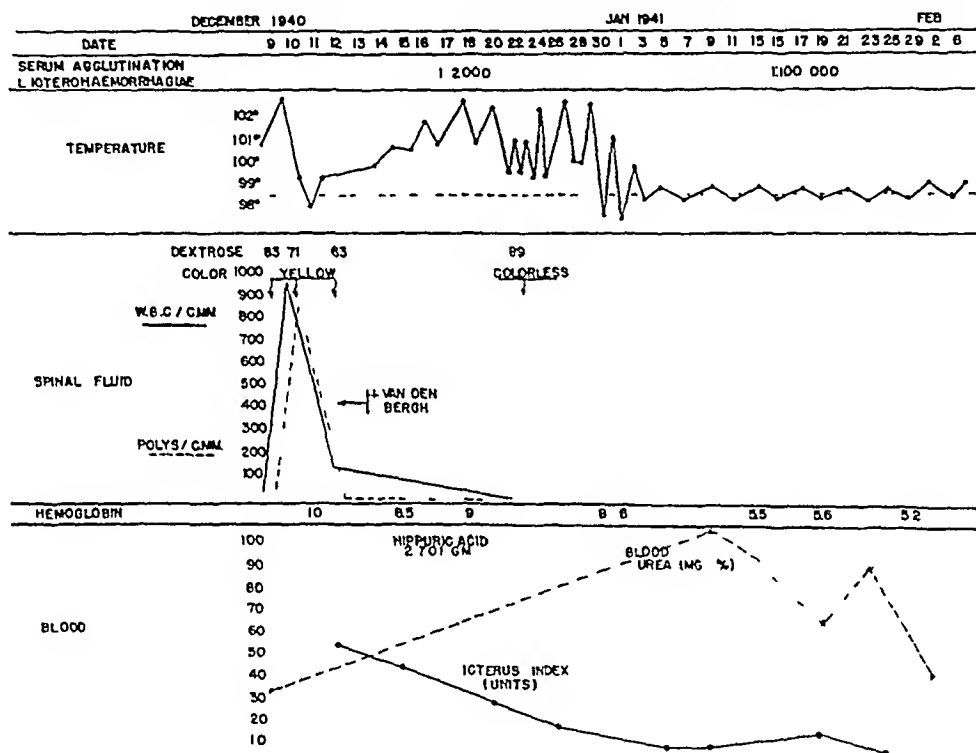


Chart 1—Data in case 1

there was an abnormal cellular reaction in the cerebrospinal fluid without clinical signs of meningeal irritation, and in 1 instance meningismus was present without pleocytosis of the cerebrospinal fluid. Lumbar puncture was not performed in 3 of the cases. All the patients presented clinical evidence of hepatitis during some phase of the illness.

#### REPORT OF CASES WITH MENINGITIS

Case 1—J. E., a Negro poultry worker aged 56, was admitted to the City of Detroit Receiving Hospital during a generalized epileptiform convulsion on Dec 9, 1940. The history, obtained from his wife, revealed that he was well until December 3, when he began to complain of generalized muscular aches. On December 5 he suffered a chill, and on

7 Davidson, L. S. P., and Smith, J. Weil's Disease in the North-East of Scotland—An Account of One Hundred and Four Cases, *Brit M J* 2 753-757 (Oct 14) 1939.

8 Goldberg, H. P., and Davens, E. D. Weil's Disease Case Presentation, *Bull Johns Hopkins Hosp* 68 112-113 (Jan) 1941.

9 Bloom, N., and Walker, H. Spirochetal Jaundice (Weil's Disease), *Virginia M Monthly* 68 192-200 (April) 1941.



the following morning a cough productive of bloody sputum was present. Shortly thereafter he became nauseated and vomited repeatedly. Convulsions commenced the day before admission. The past history was negative save that as a youth he had had a penile lesion.

Examination revealed an unconscious, dehydrated Negro man with icterus of the scleras and injection of the conjunctivas. The pupils reacted to light, and the optic fundi were normal. There were no extraocular or cranial nerve palsies. Old dried blood was present in both nares, and the lips and the tongue were dry. The neck was markedly rigid, and both Kernig and Brudzinski signs were present. The lung fields were resonant to percussion, and a few scattered coarse rales were heard. An edge of the liver, soft but sharp, and tender, was palpated 5 cm below the right costal margin. The spleen was not palpated. There was no lymphadenopathy. No paralysis was noted. The deep reflexes were equal and active, and no pathologic reflexes were elicited.

By lumbar puncture, a clear, golden yellow cerebrospinal fluid was obtained, which was under normal pressure. This contained 52 white cells per cubic millimeter, of which 50 per cent were polymorphonuclear (chart 1). Since the patient was in contact with rats at his work in a poultry house and because of the presence of jaundice, hepatomegaly, severe pain of muscles, hemorrhagic manifestations and meningeal involvement, a clinical diagnosis of Weil's disease was made. The cellular reaction in the cerebrospinal fluid, as may be seen in chart 1, reached its peak on December 10, when 990 white cells per cubic millimeter were

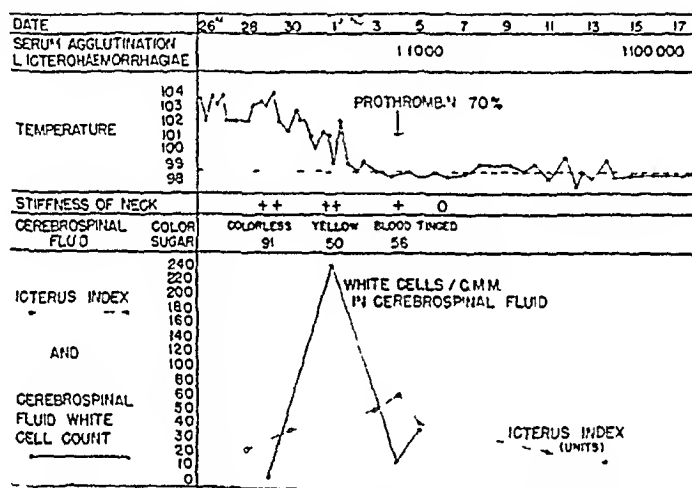


Chart 2—Data in case 2. The patient presented meningismus with pleocytosis of the cerebrospinal fluid.

present. Ninety per cent were polymorphonuclear. The fluid was still yellow on December 12, and a qualitative van den Bergh test performed on this specimen became weakly positive at the end of six minutes. The meningeal signs and symptoms cleared in several days, and the cerebrospinal fluid quickly became normal. Kahn and Kline tests of the patient's blood serum were positive but those of the cerebrospinal fluid were negative. The subsequent course of illness in the hospital was that of low grade hepatitis with progressive hypochromic, microcytic anemia. Specimens of serum obtained on Dec 19, 1940 and Jan 18, 1941, diluted 1:2,000 and 1:100,000 respectively, agglutinated *L. icterohaemorrhagiae*.<sup>10</sup> He was discharged improved Feb 10, 1941.

**CASE 2—L. D.**, an unemployed Negro youth aged 18, was admitted to the City of Detroit Receiving Hospital on May 26, 1942. His health had been good until the morning of May 25, when headache, nausea and vomiting developed. He was awakened by a true chill the following morning and was brought to the hospital a few hours later.

Examination on admission revealed an acutely ill Negro youth with a temperature of 103 F. The conjunctivas were injected, and the scleras were not icteric. The heart and the lungs were normal. There was considerable tenderness, with voluntary splinting of the abdominal wall, in the right upper quadrant. No abdominal masses were palpated. Two large infected

<sup>10</sup> The agglutinations were reported to us by Dr. Carl L. Larson, of the National Institute of Health, Bethesda, Md.; Dr. K. F. Meyer, of the Hooper Foundation of the University of California, San Francisco; and Dr. Joseph Kasper and Mrs. C. R. Broom, of the Detroit Board of Health.

blister were present on the left hand. Both the epitrochlear and the axillary lymph nodes on the left were enlarged and tender.

Bacteremia from the infection of the hand was considered, but the leukocyte count was low and blood cultures showed no growth. On May 29 slight jaundice was noted. The neck was stiff, and Kernig and Brudzinski signs were present. The possibility of complicating abscesses of the brain and the liver was considered, and a lumbar puncture was performed. The cerebrospinal fluid was completely normal. On June 1 the urine revealed albumin as well as occasional white cells and 100 red cells per high power field. By a second lumbar puncture, a clear yellow cerebrospinal fluid was obtained, which contained 242 white cells per cubic millimeter. Eighty per cent were lymphocytes (chart 2). A pellicle appeared after the spinal fluid had stood a few hours. Since repeated blood cultures were negative, and the infection of the hand had subsided almost completely, it became evident, at this point, that the jaundice, meningismus, pleocytosis of the cerebrospinal fluid, conjunctival injection and microscopic hematuria were all due to Weil's disease rather than to septicemia from the manual focus of infection. The patient when questioned carefully denied any contact with rats but admitted that he not uncommonly visited poultry houses and stood in the water while watching the employees at work.

The temperature remained near 103 F during the first four days of hospitalization and then, during the next four days, fell to normal by lysis. The icterus index reached a peak of 60 units on June 4 and then gradually fell to 16 units before discharge. Results of the remaining laboratory studies are shown in table 1. After the temperature reached normal on June 2, the rigidity of the neck disappeared, and the patient rapidly became asymptomatic. Specimens of blood serum secured on June 5 and June 16 agglutinated L icterohaemorrhagiae in dilutions of 1:1,000 and 1:100,000 respectively. The patient was discharged well on June 18.

#### REPORT OF CASES WITH CELLULAR CHANGES IN THE CEREBROSPINAL FLUID BUT WITHOUT MENINGISMUS

CASE 3—T. J., a Negro man aged 39, was admitted to the City of Detroit Receiving Hospital Aug 25, 1941. He had been well until August 19, when severe headache, marked anorexia, nausea and vomiting developed. Fever without chills commenced the next day. Urinary frequency and dysuria appeared on August 21, with the urine becoming a deep golden brown. He stated that his home was so infested with rats that it was frequently necessary for him to discard food because it was contaminated with their excreta.

Examination revealed a well developed and well nourished Negro man, who appeared older than his stated age and moderately ill. The conjunctivas were markedly injected, and the scleras were jaundiced. There was no stiffness of the neck. Kernig and Brudzinski signs were absent. The spleen and the liver were not palpated. There was moderate generalized lymphadenopathy. The course of his illness in the hospital aside from a temperature of 100 F on the day of admission was afebrile. The initial icterus index of 64 units fell to 21 before discharge. By lumbar puncture on August 29, a clear, pale yellow cerebrospinal fluid was obtained, which showed a trace of globulin. It became colorless on standing five hours. There were 14 white cells per cubic millimeter. Eighty-five per cent were lymphocytes (table 2). The Kline test was negative. A 1:100,000 dilution of the patient's serum obtained on August 27 agglutinated L icterohaemorrhagiae. He was discharged, much improved, on September 12.

CASE 4—A. J., a white slaughterhouse worker aged 52, was admitted to the City of Detroit Receiving Hospital on Nov 24, 1941. He had been well until November 17, when he experienced chilly sensations, fever, weakness and severe aching pains in the muscles of his arms and legs. He became jaundiced several days before admission.

Examination revealed a moderately ill white man with Kussmaul respiration and deep orange jaundice. The nose contained dried blood. The neck was not stiff, and Kernig and Brudzinski signs were absent. The heart and the lungs were normal aside from frequent extrasystoles. A sharp, firm edge of the liver was palpated 8 cm below the right costal margin. The spleen and the kidneys were not palpable. On November 29 a generalized erythematous, morbilliform eruption suddenly appeared on the trunk and extremities. It faded rapidly and had disappeared by December 4.

The icterus index reached a peak of 300 units on November 29 and then fell rapidly to 50 units by December 4. During this same period the urea fell from 312 to 38 mg per hundred cubic centimeters of blood. By lumbar puncture on November 29, a clear, deep golden yellow cerebrospinal fluid was obtained, which contained 0.55 mg of bilirubin per hundred cubic centimeters and gave an immediate direct but weak van den Bergh reaction. Twelve lymphocytes per cubic millimeter of cerebrospinal fluid were present (table 2). The temperature ranged between 98 F and 102 F until December 8, after which the patient was

afebrile. Specimens of serum obtained on December 8 and 23, diluted 1:1,000 and 1:100,000 respectively, agglutinated *L. icterohaemorrhagiae*. The patient was discharged improved on Jan 28, 1942.

CASE 5—E. H., a white junk collector aged 47, was admitted to the City of Detroit Receiving Hospital on Dec 6, 1941. He had been well until November 30, when chilly sensations and severe aching pains in the legs, arms and back developed. He also became nauseated and vomited repeatedly. Before admission his urine became a dark amber color but the appearance of his stools remained normal.

Examination on admission revealed a thin, jaundiced white man, who did not appear acutely ill. The scleras were icteric, and conjunctival injection was present bilaterally. The neck was not stiff, and Kernig and Brudzinski signs were not present. A soft but sharp, nontender liver edge was palpated 3 cm below the right costal margin. The spleen was not felt. The remainder of the physical examination yielded negative results.

The temperature reached 100 F during the first three days of hospitalization but was normal thereafter. The urea content of 232 mg per hundred cubic centimeters of blood found on December 8 fell to 60 in the next five days. The icterus index decreased from 94 to 40 units between December 9 and 20. By lumbar puncture on December 9, a clear golden yellow fluid was obtained. It contained 0.56 mg of bilirubin per hundred cubic centimeters. There were 93 white cells per cubic millimeter of fluid. Eighty-two per cent of these were lymphocytes (table 2). The van den Bergh reaction of the cerebrospinal fluid was direct, immediate and weak. Dark field examination of the patient's blood on December 6 failed to reveal any leptospiras. Specimens of blood serum obtained on Dec 23, 1941 and Jan 6, 1942, diluted 1:10,000 and 1:100,000 respectively, agglutinated *L. icterohaemorrhagiae*. He was discharged well Jan 17, 1942.

CASE 6—E. Tr., a white man aged 33, was admitted to the City of Detroit Receiving Hospital Dec 8, 1941. He had been well until the morning of December 1, when, while at work as a syrup mixer in a soft drink factory, he began to have aching pains in the muscles and joints of the extremities. He was confined to bed because of extreme weakness, and on December 5 epistaxis developed and his temperature rose to 103 F. Chills, anorexia, nausea and vomiting soon followed. The urine became amber in color on December 6. Jaundice was detected the day before admission.

Examination revealed a well developed and not acutely ill white man deeply bronzed from jaundice. The scleras were icteric and the conjunctivas injected, and there were several subconjunctival hemorrhages. The pharynx was slightly injected, and a few shotty cervical lymph nodes were palpable. The neck was not stiff, although there was some discomfort on flexion. A firm, sharp edge of the liver was palpated 1 cm below the right costal margin. The spleen was not palpated. Small brownish purpuric spots were present in the skin over the ankles and tibias. The muscles of both calves were tender. Kernig and Brudzinski signs were not obtained.

Characteristic leptospiras were found on dark field examination of the patient's blood on December 8, and the serum van den Bergh reaction was direct, immediate and strong. The icterus index, which was 109 units on admission, fell to 25 in the course of one week. By lumbar puncture on December 9, a clear, light golden yellow fluid was obtained, which contained 0.33 mg of bilirubin per hundred cubic centimeters of cerebrospinal fluid. There were 94 white cells per cubic millimeter, and of these 6 per cent were polymorphonuclear (table 2). The van den Bergh reaction of the cerebrospinal fluid was direct, immediate and weak. A 1:100,000 dilution of blood serum, obtained on December 23, agglutinated *L. icterohaemorrhagiae*. After a mild and afebrile hospital course, he was discharged well on December 23.

CASE 7—E. Tu., a Negro poultry worker aged 40, was admitted to the City of Detroit Receiving Hospital on Dec 16, 1941. He had been well until December 12, at which time he became weak and chilly and noted that his teeth were sore. The next day aching pains appeared in his legs. Shortly before admission to the hospital he noticed that his urine was dark amber in color. He did not inspect his stools.

Examination on admission revealed a drowsy, dehydrated Negro man, who appeared acutely ill. The conjunctivas were injected, and the scleras were deeply jaundiced. There was no stiffness of the neck, and Kernig and Brudzinski signs were absent. Neither the liver nor the spleen was palpated. Slight tenderness of a calf was present.

He experienced severe shaking chills on December 16, the day of admission, and on December 17, but thereafter the temperature did not exceed 101 F. It was normal after Jan 3, 1942. The icterus index, which was 250 units on admission, fell rapidly to 55 units on December 24. By lumbar puncture on December 17, a clear, pale lemon yellow fluid was obtained, which contained 81 white cells per cubic millimeter. Seventy-six per cent were lymphocytes (table 2). The van der Bergh reaction of the cerebrospinal fluid became weakly

positive at the end of eight minutes. Dark field examination of the patient's blood on the day of admission failed to reveal any leptospiras. A 1:100,000 dilution of a specimen of blood serum obtained Jan. 6, 1942 agglutinated *L. icterohaemorrhagiae*. He was discharged, much improved, January 14.

CASE 8—H. G., a white farmer aged 28, was admitted to the City of Detroit Receiving Hospital July 27, 1942. He had been in good health until the morning of July 17, when he experienced chilly sensations, became nauseated and commenced to vomit. These symptoms persisted, and he became progressively weaker until July 21, when severe aching pains developed in the extremities, particularly in the calves of the legs. At that time he noted that his urine was dark and his stools light, but jaundice was not detected until July 27, the day of admission. He stated that rats were present on the farm where he was employed, but he was not aware of any close contact with them.

Examination on admission revealed an acutely ill jaundiced white man with a temperature of 102 F. The conjunctivas and the pharynx were markedly injected. The neck was not stiff, but some tenderness was present on flexion. Kernig and Brudzinski signs were absent. The heart and the lungs were normal to physical examination. The blood pressure was 80 systolic and 55 diastolic. A firm, sharp edge of the liver was palpated 5 cm. below the right

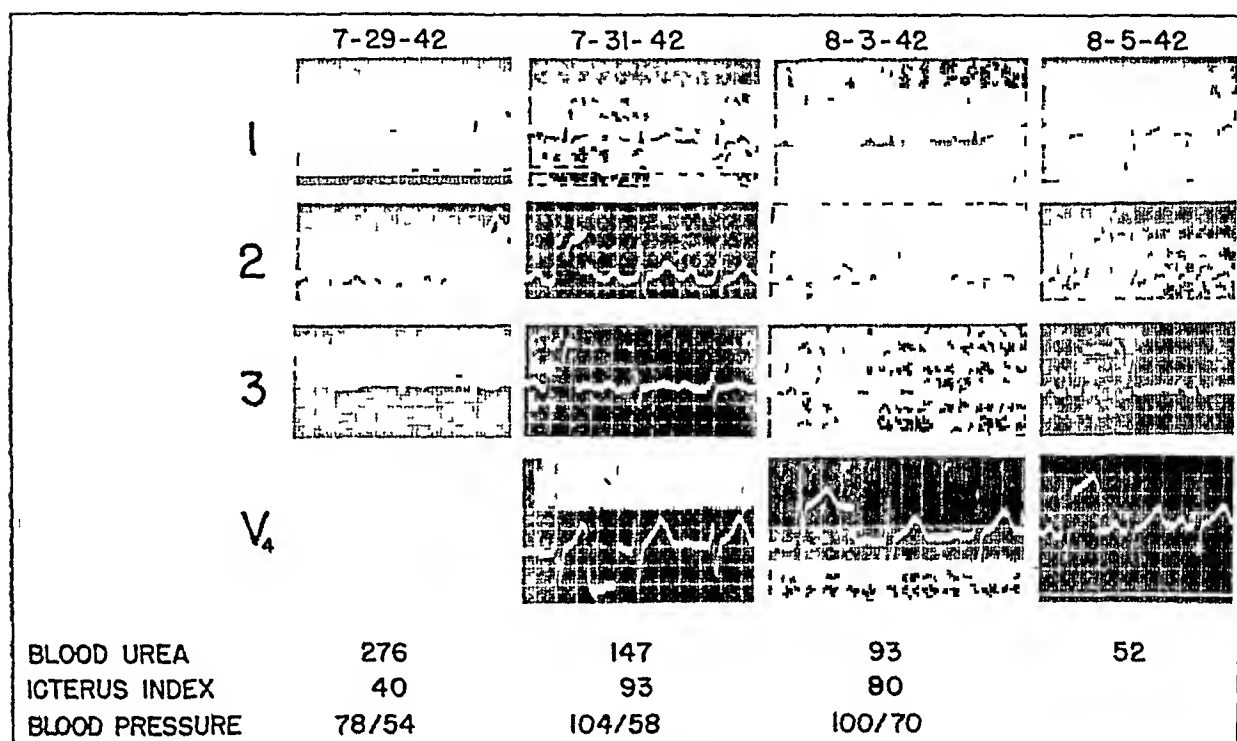


Chart 3—Electrocardiograms in case 8, showing delayed auriculoventricular conduction in Weil's disease

costal margin. The spleen was not palpated. The muscles of the extremities were very tender. Because of the characteristic history and the findings from physical examination a tentative diagnosis of Weil's disease was made.

Persistent hiccups and intense pruritus appeared on July 28. During the next twenty-four hours a moderate oliguria developed with the formation of only 6 ounces (170 cc.) of urine. At the end of this period the urea had reached 276 mg. per hundred cubic centimeters of blood (chart 3). Since necropsy studies in cases of Weil's disease<sup>2b</sup> have revealed degeneration of the adrenal cortex, the patient's hypotension and oliguria were treated with desoxycorticosterone acetate, in addition to transfusion of a half liter of blood and repeated intravenous administration of 5 per cent dextrose in saline solution. The next day, July 30, the blood pressure reached 96 systolic and 60 diastolic, and the blood urea commenced to fall (chart 3). The temperature gradually decreased, reaching normal on July 30. It remained normal until August 5, then it rose to 101 F. and continued at about this level for five days, after which it became and remained normal. By lumbar puncture on July 31, a clear, light yellow cerebrospinal fluid, was obtained, which contained 81 white cells per cubic millimeter. Eighty per cent were polymorphonuclear. The van den Bergh reaction of this fluid was direct, immediate and weak (table 2). An electrocardiogram taken on July 29 was normal save for considerably delayed auriculoventricular conduction. This was still

present on August 3, but two days later, had reverted to normal limits (chart 3) With the fall of the urea to normal, the hiccups disappeared and the remainder of the course in the hospital was uneventful A specimen of blood serum secured August 20, diluted 1 1,000,000, agglutinated L icterohaemorrhagiae He was discharged much improved August 29

CASE 9—G H, a Negro fish cutter aged 39, was admitted to the City of Detroit Receiving Hospital on Aug 8, 1942 He had been taken ill suddenly on the evening of August 6 with a chill, a sharp, stabbing pain in the left upper quadrant of the abdomen, headache, and aching pains in the muscles of the extremities He experienced a second chill the next day and a third shortly before admission, August 8 At that time he became nauseated and commenced to vomit Pain and burning on urination were experienced at the beginning of his illness, and the day before admission he noted that his urine was dark orange

He had had repeated admissions to this hospital dating back as far as 1922 He stated that during recent months his activity had been limited because of syphilitic heart disease, for which he had been receiving treatment

Examination on admission revealed a slight jaundiced Negro man, who was acutely ill Both pupils reacted to light and in accommodation The conjunctivas and the pharynx were slightly injected No stiffness of the neck was present Subcrepitant inspiratory rales were heard over the lower thirds of both lung fields posteriorly The apical impulse was palpated 11 cm to the left of the midsternal line in the fifth interspace The rate and the rhythm were regular, and systolic and diastolic blowing murmurs were heard over the entire precordium The murmurs were loudest in the second right interspace adjacent to the sternum Systolic blood pressure was 140, diastolic, 50 The abdomen was soft, with moderate tenderness in the left upper quadrant Neither the liver nor the spleen was palpated Moderate tenderness of the calves was present Kernig and Brudzinski signs were absent In view of the patient's occupation and rather characteristic history Weil's disease seemed the most likely explanation for his jaundice He also had slight heart failure due to syphilitic aortic insufficiency

By lumbar puncture on August 13, a pale yellow cerebrospinal fluid was obtained on which the van den Bergh reaction was direct, immediate and weak This contained 40 white cells per cubic millimeter, of which 90 per cent were polymorphonuclear (table 2) Positive Kline reactions were obtained on both the blood serum and the cerebrospinal fluid The colloidal gold test performed on the latter gave a paretic type of curve The patient quickly improved after admission to the hospital and received no specific treatment for his Weil's disease A specimen of blood serum obtained August 20 agglutinated L icterohaemorrhagiae when diluted 1 1,000,000 His hospital course was quite uneventful, and he was discharged improved September 13

#### REPORT OF A CASE WITH MENINGISMUS BUT WITHOUT PLEOCYTOSIS OF THE CEREBROSPINAL FLUID

CASE 10—L G, a Negro automobile washer aged 39, was admitted to the City of Detroit Receiving Hospital on Nov 29, 1941 He had been well except for a slight cold until November 27, when he noticed weakness, anorexia and severe aching pain in the back and the extremities

Examination on admission revealed an acutely ill, drowsy, dehydrated Negro man with sunken eyeballs Because of the presence of marked rigidity of the neck, as well as Kernig and Brudzinski signs, a tentative diagnosis of tuberculous meningitis was made Lumbar puncture, however, revealed a completely normal cerebrospinal fluid Weil's disease was considered at this time but was not definitely diagnosed until the appearance of slight icterus of the scleras, on December 1, two days after admission Auricular fibrillation commenced on the morning of December 2 That afternoon two physicians independently demonstrated typical leptospiras on dark field examination of the patient's blood The urea reached a peak of 420 mg per hundred cubic centimeters of blood on December 3, at which time a pericardial friction rub was heard in the fourth left interspace adjacent to the sternum Serial electrocardiograms (chart 4) confirmed the presence of auricular fibrillation and revealed elevation of the ST segments in leads II and III, characteristic of pericarditis The latter was believed to be of fibrinous type the result of uremia

Both friction rub and auricular fibrillation had disappeared by December 4 In the course of one week the urea fell to 34 mg per hundred cubic centimeters of blood During this period the jaundice became deeper, and epistaxis, bleeding from the gums and hemorrhagic herpes appeared The icterus index, which reached 150 units on December 8, gradually declined to 19 units on December 29

The blood pressure bordered on shock levels (chart 4) until a transfusion of half a liter of convalescent blood from the patient in case 4 was given on December 8 The temper-

ature fluctuated between normal and 103 F until December 15, nineteen days after the onset of his illness. It did not rise above 100 F thereafter and gradually leveled off to normal. The initial hemoglobin of 115 Gm per hundred cubic centimeters of blood slowly fell to 6 Gm and then increased slowly in response to iron therapy (chart 4). By a second lumbar puncture, December 12, a clear, yellow fluid was obtained, which contained 4 white cells per cubic millimeter and 0.6 mg of bilirubin per hundred cubic centimeters. The van den Bergh reaction of the cerebrospinal fluid was direct and immediate but weak (table 2). A 1:100,000 dilution of blood serum obtained December 23 agglutinated L. ictero-haemorrhagiae. The patient was discharged much improved Jan 26, 1942.

## REPORT OF REMAINING CASES

CASE 11—V. C., a Mexican poultry worker aged 46, was admitted to the City of Detroit Receiving Hospital on Feb 1, 1941. He had considered himself well until January 26, when

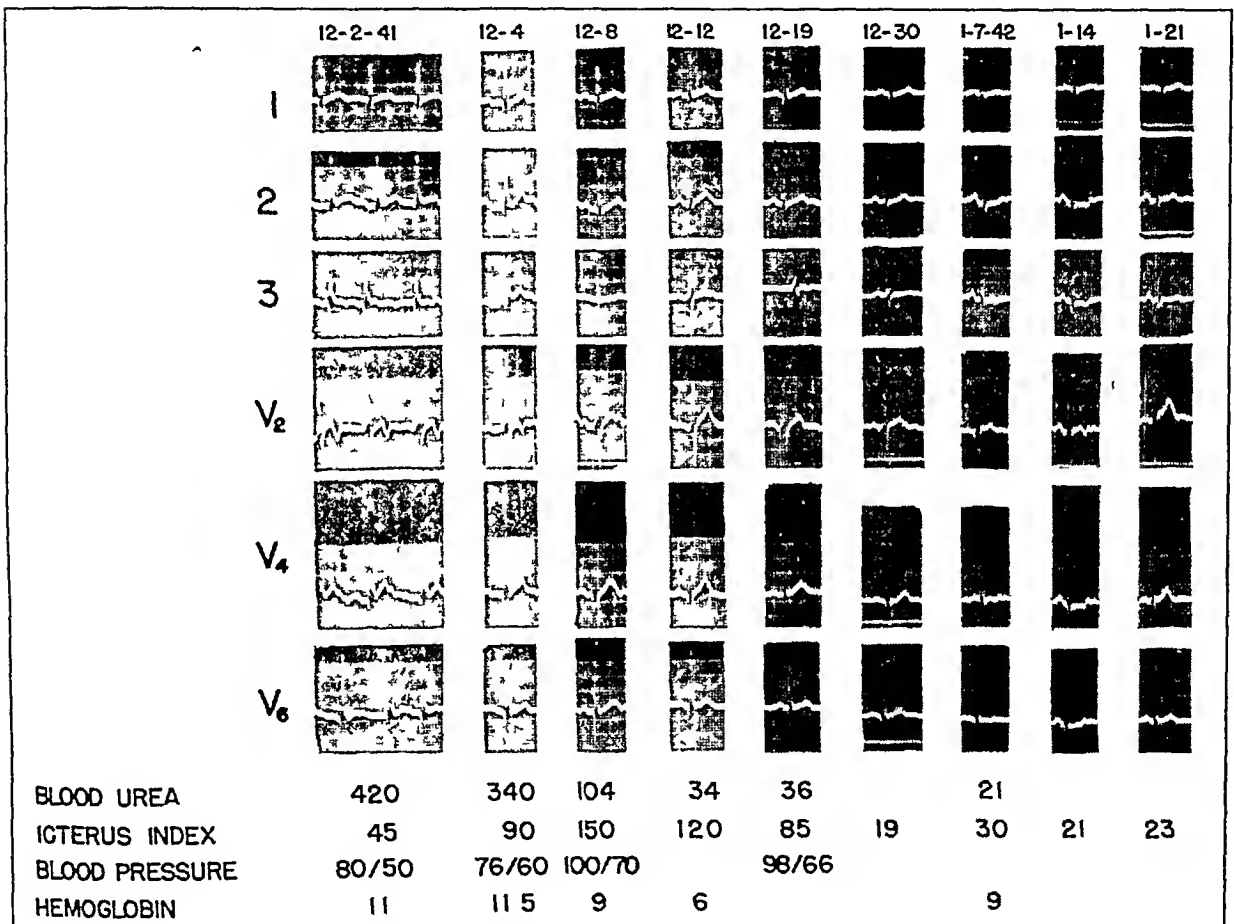


Chart 4—Electrocardiograms in case 10

severe aching pains developed in his legs, shoulders and lumbar region. Later the same day he felt feverish and vomited repeatedly. On January 30 his stools became light and his urine dark, and his skin assumed a yellow color.

Examination on admission revealed a deeply jaundiced, acutely ill Mexican man. His face and eyelids were puffy, and his scleras were a deep yellow. The neck was not stiff, and Kernig and Brudzinski signs were absent. There was a dark red maculopapular eruption over the trunk, with a purpuric eruption over the legs. Capillary resistance as determined by the Rumpel-Leede test was markedly decreased. The heart was not enlarged, and a systolic murmur was present at the apex. The abdomen was distended with fluid, and a sharp edge of the liver was ballotable 4 cm below the right costal margin. The spleen and the kidneys were not palpated.

The temperature fluctuated between 100 F and 104 F during the first week of hospitalization. It fluctuated between 99 F and 102 F during the remainder of February, leveling off to normal early in March, five weeks after the onset of the illness. At admission the icterus

index was 120 units, it gradually fell, reaching 10 units on March 7. The serum albumin, which was 2.5 Gm per hundred cubic centimeters on February 8, increased to 4.4 Gm by February 17. Inasmuch as albuminuria was slight, impaired synthesis of serum proteins, the result of damage of the liver, seemed the most likely cause. Concomitant with this increase of serum proteins the edema decreased markedly, the ascites disappeared, and the patient's weight fell from 182 to 165 pounds (from 82.5 to 74.5 Kg). The prothrombin, which was reduced to 55 per cent, returned to normal after administration of synkamin (4-amino-2-methyl-1-naphthol hydrochloride), a synthetic substance with vitamin K activity. Specimens of serum obtained on February 12 and 27, diluted 1:10,000 and 1:100,000 respectively, agglutinated *L. icterohaemorrhagiae*. The patient was discharged much improved March 10.

CASE 12—O. F., a white brewery worker aged 64, was admitted to the City of Detroit Receiving Hospital on Feb. 18, 1941. He had been in good health until February 4, when severe aching pains developed in the muscles of his legs. On February 15, while at work, he became acutely ill with nausea, vomiting, diarrhea, rectal incontinence and hallucinations. That afternoon he experienced two chills. The next morning his urine was dark, but jaundice was not noticed until the day before admission.

Examination revealed an acutely ill, semiconscious aged white man. The jaundice was deep, having somewhat of an orange hue. His lips were dry, and the tongue was dry and heavily coated. The neck was not stiff, and there was no lymphadenopathy. Kernig and Brudzinski signs were not present. The lungs were resonant, and a few inspiratory subcrepitant rales were heard at both bases posteriorly. The heart was slightly enlarged to percussion, and no murmurs were heard. The systolic blood pressure was 132, the diastolic, 105. The abdomen was distended with gas. The spleen, the liver and the kidneys were not palpated. A few small ecchymoses were present over both legs. The icterus index was 70 units, and the urea, 188 mg per hundred cubic centimeters of blood. The urine contained albumin (4+ and bile 2+) in addition to 35 white cells and 100 red cells per high power field (table 1). Treatment consisted of intravenous injection of dextrose in saline solution, administration of synkamin and transfusion of a half liter of blood from the patient in case 11, whose serum, diluted 1:10,000, agglutinated *L. icterohaemorrhagiae*. The temperature, which was 100 F on admission, steadily rose until it reached 104 F at the time of death on February 21.

At autopsy the heart was found to weigh 450 Gm. The epicardial surface and the endocardial surface over the chordae tendinae showed a few minute hemorrhages. There were numerous widely distributed pinpoint hemorrhages on the surfaces of both kidneys and the small bowel, particularly the ileum. In sections stained by a silver impregnation technique, occasional leptospiras were found in the cellular detritus in the renal tubules. None was found in the liver.

Microscopic study of the nervous system disclosed multiple localized capillary ectasias, mostly in one subcortical region, but also involving the deepest portion of the cortex. Small lymphocytic infiltrations were present in the adventitia of the subependymal vessels.<sup>11</sup>

CASE 13—F. H., a Negro odd job man aged 51, was admitted to the City of Detroit Receiving Hospital June 8, 1941. He had considered himself well until the afternoon of June 2, when he had several chills, followed by headache and intense aching pains in the extremities, particularly in the legs. The next day his eyes were yellow and marked anorexia without vomiting or abdominal pain appeared. These symptoms persisted until June 8, when, after a nosebleed, he was hospitalized. He was not aware of any close contact with rats or their excreta.

The patient was a well developed and well nourished Negro man, who did not appear acutely ill. His neck was not stiff, and Kernig and Brudzinski signs were absent. The remainder of the examination gave negative results aside from marked jaundice of the scleras and a firm, sharp, slightly tender edge of the liver, which was palpable 1.5 cm below the right costal margin. Kline and Kahn tests of the patient's serum were positive. Blood serum obtained on June 9 and August 21, diluted 1:1,000 and 1:100,000 respectively, agglutinated *L. icterohaemorrhagiae*. By lumbar puncture two weeks after admission, a completely normal cerebrospinal fluid was obtained. On admission the urea was 204 mg per hundred cubic centimeters of blood and the icterus index 176 units. They gradually fell to normal. A finely papular pruritic eruption appeared over the trunk on June 18 and faded within a few days. The entire course of his illness in the hospital was mild and practically afebrile. The patient was discharged, much improved, on July 10.

<sup>11</sup> This pathologic report is included with the permission of Dr. Osborne A. Brines, pathologist at the City of Detroit Receiving Hospital and associate professor of pathology at the Wayne University College of Medicine.



TABLE 1—Laboratory Studies in Weil's Disease

Patient Case	J R	L D	T J	A J	R H	E Tr	R Tu	H G	G H	L G	V O	O F	F H
1	1	2	3	4	5	6	7	8	9	10	11	12	13
Urine													
Albumin (range)	0.2+	0.1+	0 Tr	Slt Tr 3.1	Slt Tr 2.1	2.1 Tr	Tr 1.1	0.3+	0.2+	1-4 Slt Tr	0.2+	4+	0 Tr
Red cells (range per high power field)	25.0	0.100	1.0	Oec 0	0	0	0 Oec	0.2	0.3	Many 0	0	100	0
White cells (range per high power field)	0.20	0.3	0.5	15.0	90.0	18.3	0.10	0.120	0.8	50.0	0.20	35	0.12
Urobilinogen (highest concentration)	1.150	1.50	1.300	1.170	1.10	1.20	1.10	Trace	1.90	1.100	1.90	—	1.150
Blood													
Agglutinins (highest titer)	1 100,000	1 100,000	1 100,000	1 100,000	1 100,000	1 100,000	1 100,000	1 1,000,000	1 1,000,000	1 100,000	1 100,000	—	1 100,000
Urea (highest value, mg per 100 cc)	108	35	39	312	232	52	90	276	59	420	64	188	304
White cells (highest count per cu mm)	22,850	9,500	28,300	25,650	21,600	19,200	16,040	20,900	12,000	18,250	27,150	19,100	19,100
Polymorphonuclears (highest %)	81	93	88	94	86	83	93	95	76	95	88	93	93
Hemoglobin (Gm per 100 cc)													
Initial	10	12	13	12	11.5	13	9.5	11	14	11.5	10	16	12
Lowest	5.2	9	10	5.5	10.5	12	8.5	11	12	6	8.5	14.5	8
Prothrombin (lowest %)	76	70	57	81	60	77	—	60	59	55	55	66	80
Icterus index (highest value, units)	54	60	64	300	94	109	250	93	115	150	120	70	176
Serum bilirubin (highest value, mg per 100 cc)	5.1	5.0	—	27.5	6.5	10	15.5	8.6	—	9.2	10.8	—	—
Van den Bergh reaction	Direct immediate strong	Direct immediate strong	—	Direct immediate strong	Direct immediate strong	Direct immediate strong	Direct immediate strong	Direct immediate strong	—	Direct immediate strong	Direct immediate strong	—	—
Platelets (lowest count per cu mm)	—	—	—	226,000	30,000	153,000	—	121,770	—	56,000	534,870	—	—



## COMMENT

The symptom complex of Weil's disease is often sufficiently characteristic to permit the condition to be diagnosed clinically. The onset is abrupt, with chills, fever, headache, muscular pains and weakness. In the present series a true chill

TABLE 2—*Cerebrospinal Fluid in Weil's Disease*

		Cerebrospinal Fluid									Blood	
Patient	Case	Day of Illness	Rigidity of Neck	Color	Bili rubin, Mg per 100 Ce	Van den Bergh Reaction	Glob ulin	White Cells per Ce	% of Poly morpho nuclear Cells	Sugar, Mg per 100 Ce	Icterus Index, Units	Bili rubin, Mg per 100 Ce
Cases with Meningismus												
J E	1	7	++++	Golden yellow	—	—	0	52	50	83	—	—
		8	++++	Golden yellow	—	—	0	990	90	71	—	—
		10	+++	Pale yellow	—	Direct, immediate, weak	Slight trace	142	18	63	54	5.1
		19	0	Color less	—	—	0	13	5	89	19	—
L D	2	3	++	Color less	—	—	0	1	0	61	35	—
		6	++	Yellow	—	—	Faint trace	242	19	50	—	—
		9	+	Blood tinged	—	—	—	12	—	56	60	5
		10	0	Blood tinged	—	—	—	38	0	—	40	3
L G	10	3	+++	Color less	—	—	0	2	0	91	—	—
		16	+	Golden	0.6	Direct, immediate, weak	0	4	0	81	120	11
Cases without Meningismus												
T J	3	11	0	Pale yellow	—	—	Slight trace	14	15	65	64	—
A J	4	13	0	Golden yellow	0.50	Direct immediate, weak	0	12	0	105	300	21.2
E H	5	10	0	Golden yellow	0.56	Direct, immediate, weak	+	93	18	77	94	9.6
E Tr	6	10	0	Pale yellow	0.33	Direct, immediate, weak	Slight trace	94	6	67	109	8.3
E Tu	7	6	0	Lemon yellow	Too low to read	Direct, immediate, 8 minutes	Slight trace	81	24	59	250	15.5
T H	13	21	0	Color less	—	—	0	0	0	83	20	—
H G	8	10	0	Pale yellow	Too low to read	Direct, immediate, weak	0	81	80	59	93	8.6
G H	9	8	0	Pale yellow	Too low to read	Direct, immediate, weak	+++	40	90	63	115	—

occurred in 6 cases, chilly sensations in several more and fever in all 13. Muscular pains, headache, nausea and weakness each occurred in 11. Emesis was present in 10 and cough and abdominal pain each in 6. External bleeding was observed in 3 and convulsions in 1. The occurrence of symptoms referable to the urinary tract was also of interest, for 5 patients experienced frequency and 3 dysuria. Four patients were troubled with persistent hiccups. In each of these patients there was marked retention of urea, and the singultus stopped as the blood urea approached normal.

Physical examination revealed jaundice in all 13 cases, tenderness of the muscles of the calves in 12, conjunctival injection in 11, abdominal tenderness in 9, hemorrhagic manifestations in 8, enlargement of the liver in 8, skin eruption in 3, meningismus in 3, generalized lymphadenopathy in 2, iridocyclitis in 1 and auricular fibrillation associated with pericardial friction rub in 1. Abdominal tenderness when present was in the right upper quadrant and occurred in those cases with enlargement of the liver. It was thought to be due to the distention of Glisson's capsule.

Perusal of charts 3 and 4 reveals that the delayed auriculoventricular conduction in case 8 (chart 3) and the pericarditis and auricular fibrillation in case 10 (chart 4) each occurred during the height of the illness, when retention of urea was most marked. While it is possible that the uremia was responsible for the pericarditis, it seems more likely that the auricular fibrillation and the disturbance of conduction were due to the effect on the heart of the spirochetes or their toxic products, for we have not noted such cardiac involvement in uremia from other causes.

The significant findings in the blood and the urine are summarized in table 1. There is still uncertainty as to the course of the hemorrhagic manifestations in this disease. The prothrombin percentages, as determined by the method of Quick,<sup>12</sup> were appreciably decreased in most instances. They did not, however, reach levels sufficiently low to account for the hemorrhagic manifestations. In the 3 cases in which platelet counts were performed, thrombopenia was not marked enough to account for hemorrhage. A positive Rumpel-Leede test in case 11 indicated the presence of capillary damage. This test also was negative in the other cases with hemorrhage. A considerable leukocytosis, with counts usually between 18,000 and 30,000, was present in 11 of the 13 cases. There was a distinct shift to the left in the leukocytes of the peripheral blood as well as in the bone marrow in the 2 patients subjected to sternal puncture. In 4 patients a marked hypochromic, microcytic anemia developed. Albuminuria was present in every case. Microscopic study of the urine not uncommonly revealed white cells, red cells or both. Levels of urinary urobilinogen were extremely variable.

Marked retention of the nitrogenous products of the metabolism of protein was common in this series as in others of Weil's disease. There has been some question as to the genesis of azotemia in this condition.<sup>13</sup> Reference to table 1 shows that frequently the blood urea was higher in the moderately jaundiced patients than in those more deeply icteric. The cases illustrated in figures 3 and 4 each showed a precipitous fall in blood urea concomitant with a rise in icterus index. As a result of these observations we believe that the renal damage, which was obviously quite transient, was due to the effect of the spirochetes or their products, rather than to cholemia.

Three of the 13 patients (cases 1, 2 and 10) exhibited clinical signs of meningeal involvement. These consisted of marked stiffness of the neck, Kernig and Brudzinski signs, headache and vomiting. The patient in case 1 had in addition generalized epileptiform convulsions. The cell count on the cerebrospinal fluid of this patient reached a peak of 990 cells per cubic millimeter of fluid. Polymorphonuclear cells predominated early and lymphocytes later (chart 1). Case 10, in which considerable rigidity of the neck preceded the appearance of jaundice, was mistaken for a case of tuberculous meningitis on admission of the patient to the hospital. This case demonstrates that marked meningismus may exist without any abnormality of the

12 Quick, A. J. The Nature of Bleeding in Jaundice, *J. A. M. A.* **110** 1658-1662 (May 14) 1938.

13 Merklen, P., and Lioust, C. L'azotemie dans les icteres infectieux, *Bull. et mém. Soc. med. d'hôp. de Paris* **40** 1865-1916 (Nov. 24) 1916.

cerebrospinal fluid other than an increase in pressure. Similar American cases have been reported by Haschec and Tobey<sup>14</sup> and Ashe, Pratt-Thomas and Kunpe<sup>2b</sup>. Seven of the 8 remaining cases in which the patient was subjected to lumbar puncture showed an increased cell count for the cerebrospinal fluid in spite of the absence of clinical signs of meningeal involvement. In 5 of these the protein content of the cerebrospinal fluid was also increased. It is of interest that such changes occurred without clinical symptoms, whereas in case 10 clinical meningismus occurred without abnormality of the cerebrospinal fluid. Inasmuch as the lumbar punctures in this case were performed on the third and sixteenth days, the possibility of a transient pleocytosis of the cerebrospinal fluid in the interim cannot be excluded. The dextrose content of the cerebrospinal fluid was essentially normal in all of the cases studied.

A yellow cerebrospinal fluid was obtained in 10 of the 11 cases in which lumbar puncture was performed. In some of these the yellow color faded somewhat on standing, and in case 3 it disappeared completely. In 8 cases the cerebrospinal fluid gave a positive qualitative van den Bergh reaction, and in 4 it was possible to measure the bilirubin content quantitatively. This proves to our satisfaction that at least in Weil's disease bilirubin in appreciable quantities passes the meningeal barrier. Since we found more bilirubin in the cerebrospinal fluids of patients with Weil's disease than in patients jaundiced to like degrees in other diseases, we agree with Dragert's<sup>15</sup> hypothesis that the permeability of the diseased meninges in this condition is increased.

#### SUMMARY

Thirteen cases of Weil's disease are reported. In 2 both clinical and laboratory evidence of meningitis was observed, in 7 there was an abnormal cellular reaction in the cerebrospinal fluid without clinical signs of meningeal irritation, and in 1 meningismus was present without the cerebrospinal fluid showing pleocytosis.

Cell counts on the cerebrospinal fluid may reach 1,000 or more per cubic millimeter. Polymorphonuclear cells predominate early and lymphocytes later. The dextrose content of the cerebrospinal fluid is not altered. Yellow discoloration of the cerebrospinal fluid is common in Weil's disease. It is at least in part due to bilirubin.

Marked retention of urea is frequent.

Pericarditis, auricular fibrillation or disturbances of conduction may occur in hearts previously normal.

The plasma prothrombin, although appreciably decreased in most instances, usually does not reach levels sufficiently low to account for the hemorrhagic manifestations.

Anasarca, the result of hypoproteinemia, may develop.

Immunotransfusions may be of value in treatment and are worthy of a more extended trial.

City of Detroit Receiving Hospital

14 Haschec, W., and Tobey, F. J. A Case of Weil's Disease, *J. A. M. A.* **113** 1319-1321 (Sept 30) 1939.

15 Dragert, E. Beitrag zur pathologischen Anatomie der Weilschen Erkrankung, *Virchows Arch f path Anat* **292** 452-464 (June) 1934.

# PENTOSURIA ASSOCIATED WITH DIABETES MELLITUS

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There has been no evidence to show that essential pentosuria is related in any way to diabetes mellitus, and no complete report of their combined occurrence can be found in the literature<sup>1</sup> In the first case presented here the patient was suffering from both essential pentosuria and diabetes mellitus By way of comparison a case of uncomplicated essential pentosuria is also reported

Essential pentosuria is a hereditary abnormality of metabolism characterized by continuous excretion of small amounts of pentose in the urine, unaffected by alterations in the diet The first case of this disorder was reported by Salkowski and Jastrowitz<sup>2</sup> in 1892 Since then reports of more than 170 cases have appeared in the literature The incidence of this disorder in the general population is estimated by Blatherwick<sup>3</sup> to be 1/50,000

The pentose excreted has been found in most instances to be levorotatory xylulose, formerly called *l*-xyloketose Enklewitz and Lasker<sup>4</sup> have shown that the administration of *d*-glucuronic acid caused an increased excretion of xylulose, and they were in this way led to believe that glucuronic acid is a precursor of xylulose Schultz<sup>5</sup> has confirmed this work and suggested that the reaction may take place in the kidney

Pentosuria can be classified into two types, alimentary and essential Alimentary pentosuria is the transient excretion of pentose in the urine following the ingestion of certain foods, particularly cherries, grapes, prunes, pears, blackberries, strawberries, wine and beer These foods contain pentosans, some of which are excreted in the urine in the form of pentose In many cases pentosuria which has been designated transient, intermittent, occasional or acquired falls under this heading of alimentary pentosuria

The criteria for the diagnosis of essential pentosuria are as follows (1) the continuous excretion of small amounts of pentose in the urine, unrelated to diet, (2) absence of symptoms, (3) history of hereditary pentosuria when obtainable, and (4) a normal dextrose tolerance curve unless there is associated diabetes mellitus

For the identification of pentose the following tests should be performed (1) the reduction of copper salt solutions, (2) test for absence of fermentation, (3) the

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1 Since this article has been written, a case of pentosuria and diabetes mellitus has been reported (Moss, R E, and Walker, B S Pentosuria and Diabetes Mellitus, J A M A **120** 25 [Sept 5] 1942)

2 Salkowski, E, and Jastrowitz, M Ueber eine bisher nicht beobachtete Zuckerart im Harn, Centralbl f d med Wissensch **30** 337, 1892

3 Blatherwick, N R Xylulosuria, in Blumer, G Practitioners Library of Medicine and Surgery, New York, D Appleton-Century Company, Inc, 1938, vol 13

4 Enklewitz, M, and Lasker, M The Origin of *l*-Xyloketose (Urine Pentose), J Biol Chem **110** 443, 1935

5 Schultz, J C Onderzoekingen over pentosurie, Amsterdam, N V, Uitgevers-Maatschappij "Kosmos," 1938

test with Bial's reagent (orcinol, hydrochloric acid and ferric chloride), (4) the aniline acetate test<sup>6</sup> and (5) preparation of xylulosazone. Familiarity with the peculiar characteristic behavior of pentose with the copper reducing salts is helpful. It is commonly observed that when urine containing pentose is heated over a flame with copper salts, reduction does not take place immediately, as it does with dextrose. However, xylulose will reduce copper salt solutions at room temperature.<sup>7</sup> This is a valuable confirmatory test. Although the reaction will be obtained in two to three hours or less, it is a practice in some clinical laboratories to allow the solution to stand overnight, the reaction being noted the following morning.

Lasker and Enklewitz<sup>7</sup> have also found that a yellow precipitate is formed with xylulose in Benedict's solution at 55 C in ten minutes. Furthermore, urine containing xylulose retains its reducing powers indefinitely on standing, which is not true of urine containing dextrose, since the latter sugar undergoes glycolysis.

If the tests just listed yield positive reactions and the confirmatory reactions with the copper salt solutions are present, it is hardly necessary to attempt to obtain the specific osazone.

The daily excretion of pentose usually does not exceed 2 to 4 Gm. Occasionally, smaller amounts are obtained. Solis-Cohen and Gershenfeld<sup>8</sup> reported a case in which an elderly man with essential pentosuria had been observed for twenty-seven years and at the end of this time was excreting 10.5 Gm of pentose daily. Whatever the amount excreted, it remains constant for each person with small variations dependent on the total output of urine for twenty-four hours.

#### REPORT OF TWO CASES

##### CASE 1—*Essential pentosuria associated with diabetes mellitus*

L. M., a Russian Jew aged 52, was originally seen in the orthopedic clinic of the hospital on Dec. 1, 1937, complaining of cramps in the calves of the legs, occurring mainly at night. The blood pressure at this time was 115 systolic and 70 diastolic, measured in millimeters of mercury. Calcium salts were prescribed, and he was not seen again until Nov. 8, 1940, when he complained of substernal pain which was increased with exertion. His weight was found to be 174 pounds (79 Kg). The blood pressure was 155 systolic and 90 diastolic in millimeters of mercury. Examination of a specimen of urine at this time yielded the following data: specific gravity, 1.018; sugar, a trace (Benedict's solution); acetone, none; and albumin, none.

Microscopic examination of the urine revealed occasional blood cells, both white and red. The urine was retested with Benedict's quantitative solution and was found to contain 0.8 per cent sugar. The cramps in the calves of the legs were still present. Examination of the lower extremities failed to reveal any evidence of peripheral vascular disease. When the patient was examined again, in September 1941, the blood pressure was 160 systolic and 105 diastolic in millimeters of mercury and continued at about this level on his subsequent visits to the clinic. The weight was reduced to 165 pounds (75 Kg). The patient was seen periodically during 1941 and complained of frequent attacks of substernal pain lasting ten minutes and associated with dyspnea on exertion. A specimen of urine tested in December 1941 with Benedict's quantitative solution contained 0.5 per cent sugar. The blood pressure at this time was 190 systolic and 110 diastolic in millimeters of mercury. When the patient was seen again, in March 1942, it was decided to study the urine for the nature of the reducing substance. The urine was found to contain pentose. No dextrose was present in individual or in twenty-four hour specimens of urine. Samples of blood drawn while the patient was fasting contained 150 mg of sugar per hundred cubic centimeters on two occasions. Repeated examinations of single specimens of urine revealed between 0.15 and 0.3 per cent pentose but no dextrose. Dextrose tolerance curves obtained on two occasions (100 Gm of dextrose fed) were of the diabetic type (table 1).

<sup>6</sup> Reimer, M. *Manual of Clinical Chemistry*, New York, Interscience Publishers, Inc., 1941.

<sup>7</sup> Lasker, M., and Enklewitz, M. A Simple Method for the Detection and Estimation of *l*-Xyloketose in Urine, *J Biol Chem* **101** 289, 1933.

<sup>8</sup> Solis-Cohen, S., and Gershenfeld, L. Essential Pentosuria of Twenty-Eight Year's Standing, *Am J M Sc* **192** 610, 1932.

The sugar found in the urine was not fermented by bakers' yeast. It reduced copper salt solutions in two to three hours at room temperature and in ten minutes at 55 C. Positive reactions with Bial's reagent and a positive reaction with aniline acetate were obtained with every specimen, and xylulazone was obtained with phenylhydrazine.

*Comment*—This patient was apparently suffering from mild diabetes mellitus but did not experience any of the cardinal symptoms of the disease. At the same time, pentose was being excreted in constant amounts persistently in the urine and all the criteria for the diagnosis of essential pentosuria were satisfied. It is of interest that in this case the nature of the reducing substance in the urine was studied before the blood sugar level was obtained. If the blood sugar level had been obtained first, the patient might have been considered solely to have mild diabetes, and investigation of the nature of the urinary sugar might not have been undertaken.

Fischer and Reiner<sup>9</sup> studied 4 children with essential pentosuria and obtained dextrose tolerance and xylose tolerance curves. They determined the total blood sugar levels, the dextrose was then fermented, and the nondextrose reducing substances were obtained in this way. After xylose was fed, its level in the blood

TABLE 1—*Dextrose Tolerance of a Patient with Diabetes Mellitus and Associated Essential Pentosuria (Case 1)*

Date	Time in Relation to Ingestion of 100 Gm. of Dextrose	Blood Sugar, Mg./100 Cc.	Urine Sugar, Percentage
4/2/42	Before (patient fasting)	181	Trace
	½ hour after	276	1.8
	1 hour after	306	6.6
	1½ hours after	222	10.0
	2 hours after	161	2.2
4/20/42	Before (patient fasting)	160*	0.2
	½ hour after	270*	0.8
	1½ hours after	310*	5.5
	2½ hours after	250*	6.6

\* All specimens of blood contained 20 mg. of nonfermentable nondextrose reducing substances per hundred cubic centimeters.

could be determined by noting the increase in the nondextrose reducing substance over values obtained on blood drawn while the patient was fasting. They found that the feeding of dextrose had no effect on the urinary excretion of xylose, while the dextrose tolerance curve remained unaltered when xylose was fed. The total nondextrose reducing substances remained the same in the blood of normal persons as well as in that of persons with essential pentosuria. The nondextrose reducing substances in the blood in this case were determined and found to remain constant at 20 mg. per hundred cubic centimeters in all specimens taken during the determination of the dextrose tolerance curve (table 1). Thus the elevation of the blood sugar was due to the elevation of the dextrose portion of the total sugar and not of the nondextrose reducing substances.

#### CASE 2—*Essential pentosuria*

A. L., a Russian Jew aged 41, was admitted to the medical clinic on Aug. 29, 1941, complaining of attacks of weakness and faintness lasting a few seconds and occurring for the past eight months. There had been a loss of 9 pounds (4 Kg.) in weight over a five month period. Examination failed to reveal any major abnormalities. There was a short, rough systolic murmur at the apex of the heart. The blood pressure was 126 systolic and 78 diastolic measured in millimeters of mercury. The first examination of the urine yielded the following data:

<sup>9</sup> Fischer, A. E., and Reiner, M. Pentosuria in Children, *Am J Dis Child* 40:1193 (Dec.) 1930.

specific gravity, 1.028, albumin, none, and sugar, present (3 plus) In September 1941 a sample of blood drawn while the patient was fasting contained 98 mg of sugar per hundred cubic centimeters The dextrose tolerance test (100 Gm of dextrose fed) yielded a high normal curve which returned to the fasting level in two hours On the basis of these data a tentative diagnosis of renal glycosuria was made The dextrose tolerance test was repeated in June 1942, and the curve was found to be entirely normal (table 2) The urine was studied, and the reducing substance was proved to be xylulose

## COMMENT

Essential pentosuria should be suspected when small amounts of a reducing substance are found constantly in the urine of a person who has normal blood sugar levels and no diabetic symptoms A pentose can be identified by the special tests that have been described

Reactions similar to those obtained with pentose in the urine are also given by glucuronates These substances may be present in small quantities in normal urine and may be present in larger amounts after the ingestion of certain drugs, such as chloral hydrate, camphor, menthol, oil of turpentine, phenol, acetanilid and some alkaloids Glucuronates are usually present in conjugated form, resulting from combination of an ingested drug and glucuronic acid Protas<sup>10</sup> noted an example of "toxic pentosuria" in a person addicted to morphine When the

TABLE 2—*Dextrose Tolerance of a Patient with Essential Pentosuria (Case 2)*

Date	Time in Relation to Ingestion of 100 Gm of Dextrose	Blood Sugar Mg /100 Cc
9/16/41	Before (patient fasting)	115
	½ hour after	190
	1 hour after	160
	1½ hours after	112
	2 hours after	83
6/11/42	Before (patient fasting)	110
	½ hour after	155
	1 hour after	126
	1½ hours after	106
	2 hours after	91

morphine was withdrawn, the pentosuria disappeared It may well have been due to glucuronates

Conjugated glucuronates do not give reactions in all the tests for pentose Free glucuronic acid, on the other hand, gives a reaction in the majority of these tests and as a result is almost indistinguishable from pentose, Glucuronic acid is set free after prolonged heating or in the presence of the concentrated acids used in the Bial and the aniline acetate test

It is apparent that conjugated glucuronates or free glucuronic acid will be confused with pentose unless careful observation reveals that all the tests do not readily yield positive results In addition, the excretion of glucuronates may be directly related to the ingestion of a drug and can in this way be controlled

There are no known symptoms that are considered the direct result of essential pentosuria Garrod<sup>11</sup> has said that if the metal-reducing tests were not everyday practice in medical work, there would be no symptom by which the existence of pentosuria could be suspected Margolis<sup>12</sup> found that some of his patients with pentosuria suffered from migraine In the 2 cases presented here the patients did not have symptoms of migraine, and there is no mention of migraine in the majority of reports of cases of essential pentosuria

10 Protas, M Pentosuria, *South Med & Surg* **96** 154, 1934

11 Garrod, A E *Inborn Errors of Metabolism*, ed 2, London, Milford, 1923

12 Margolis, J I *Chronic Pentosuria and Migraine*, *Am J M Sc* **177** 348, 1929

*Essential Pentosuria and Renal Glycosuria*—The diagnosis usually made when essential pentosuria is not recognized is renal glycosuria (renal diabetes, or “benign” glycosuria). Two of the 3 cases of essential pentosuria reported by Marble<sup>13</sup> were originally considered to have been instances of renal glycosuria. Enklewitz and Lasker<sup>14</sup> reported the occurrence of essential pentosuria in twins, one was treated in childhood for renal diabetes and the other for “juvenile diabetes.” Many other reports of cases of essential pentosuria reveal that the usual diagnosis prior to the discovery of the true nature of the sugar was renal diabetes.

In both renal glycosuria and essential pentosuria, both of which are rare, the excretion of the sugar is constant and is essentially independent of diet. In both conditions the dextrose tolerance curves are normal, except in rare instances when diabetes mellitus may be associated coincidentally<sup>15</sup>. The amount of excretion for each individual specimen of urine is usually under 1 per cent in essential pentosuria and over 1 per cent in renal glycosuria. In both disorders, the symptoms of diabetes are absent and there is no progression to diabetes mellitus. Finally, the nature of the reducing substance is different, and the fermentation test will indicate whether it is dextrose or pentose. Jones and Sussman<sup>16</sup> emphasized that in both conditions the renal and the pancreatic functions are normal.

*Essential Pentosuria and Diabetes Mellitus*—Ever since the original article on pentosuria by Salkowski and Jastrowitz<sup>2</sup> in 1892 the question had arisen whether there was any relation between essential pentosuria and diabetes mellitus. Gaird<sup>11</sup> stated that he considered essential pentosuria one of the “inborn errors of metabolism” along with alkaptonuria, cystinuria, porphyrinuria and congenital steatorrhea.

The early literature on the subject is confusing. Several authors reported finding pentosuria frequently in persons with severe diabetes (Kulz and Vogel,<sup>17</sup> Pedrazzini<sup>18</sup> and Voit<sup>19</sup>). Thus Kulz and Vogel<sup>17</sup> were able to find in the urine of some of their patients with severe diabetes, in addition to a glucosazone, an osazone with the melting point and the nitrogen content of pentosazone. However, they required several liters of urine to obtain a small yield of the substance. Voit<sup>19</sup> admitted the difficulty of separating chemically small amounts of pentose from dextrose when both are present in the same specimen of urine. He reported finding an osazone with the melting point of pentosazone in the urine of 12 of the 14 patients with severe diabetes whom he studied. Bendix<sup>20</sup>, Joslin and associates<sup>21</sup>, Enklewitz and Lasker, Blatherwick, one of us (M. R.), and many others have searched for pentose in the urine of persons with diabetes and have been unable to detect it in any constant amount in mildly or severely diabetic persons. It is assumed that the substance that was considered a pentose by these earlier investigators was probably a glucuronate.

13 Marble, A. Chronic Essential Pentosuria, *Am J M Sc* **183** 827, 1932.

14 Enklewitz, M., and Lasker, M. Pentosuria in Twins, *J A M A* **105** 958 (Sept. 21) 1935.

15 Curran, J. A., and Mills, C. A. Report of a Case of Renal Diabetes Associated with Diabetes Mellitus, *J Lab & Clin Med* **13** 646, 1928.

16 Jones, H. W., and Sussman, W. Renal Glycosuria and Pentosuria, *Am J M Sc* **173** 513, 1927.

17 Kulz, E., and Vogel, J. Ueber das Vorkommen von Pentosen im Harn bei Diabetes Mellitus, *Ztschr f Biol* **14** 185, 1895.

18 Pedrazzini, F. La ricerca dei pentosi nelle urine, pentosurie e pseudopentosurie, *Gior d r Soc ital d'ig* **25** 241, 1903.

19 Voit, W. Ueber das Vorkommen von Pentosen in diabetischen Harnen, *Ztschr f phys u diatet Therap* **12** 659, 1908-1909.

20 Bendix, E. Ein Fall von Pentosurie, *Munchen med Wchnschr* **50** 1551, 1903.

21 Joslin, E. P., Root, H. F., White, P., and Marble, A. *The Treatment of Diabetes Mellitus*, ed 7, Philadelphia, Lea & Febiger, 1940.



There are many individual case reports in the literature concerning patients with diabetes mellitus who in the course of their illness were discovered to have pentose in the urine intermittently (Kaplan,<sup>22</sup> d'Amato<sup>23</sup> and Zlataroff<sup>24</sup>) In the case reported by Kaplan,<sup>22</sup> the excretion of "pentose" was not constant and many specimens of urine were free of "pentose" In the case reported by Rosenbloom,<sup>25</sup> "pentose" was encountered on one occasion and lactose was also found in the urine In these and other cases the reports indicate conclusively that the substances found were appearing in the urine only intermittently and were not proved to be pentose

Joslin and associates<sup>21</sup> in spite of a careful search for cases of essential pentosuria have recorded only 9 instances of this disorder In 1 case, the patient had occasional blood sugar values slightly above normal and the condition has been difficult to classify Other than this questionable case they have not encountered any instances of the association of diabetes mellitus and essential pentosuria Blatherwick<sup>26</sup> has observed 1 case of this kind, but it has been incompletely studied and has not been reported In this case only one specimen of urine had been examined, and it was found to contain 2.03 per cent dextrose and 0.16 per cent pentose

The clinical importance of recognizing essential pentosuria has been stressed many times before Patients with essential pentosuria require no treatment except for the reassurance that they do not have diabetes mellitus They should be told the nature of the reducing substance in their urine to facilitate future examinations in new locations and acquainting physicians under whose care they may come with the diagnosis In addition, when the rare coincidental association of diabetes mellitus and essential pentosuria exists, the failure to discover both will result in difficulties in treatment The failure to recognize the diabetes mellitus will carry along with it the dangers of developing complications common in untreated diabetes mellitus of long standing On the other hand, failure to recognize the presence of essential pentosuria will cause confusion, as sugar will always be present in the urine despite seemingly adequate control with diet and insulin

The harm that is done to a person who has essential pentosuria and is treated for diabetes mellitus is obvious

#### SUMMARY AND CONCLUSIONS

Two cases of essential pentosuria are presented and discussed

The coexistence of diabetes mellitus with essential pentosuria was discovered in 1 of these cases

Essential pentosuria and diabetes mellitus are distinct entities and seem to bear no relation to each other

Dr Louis J Soffer assisted us during this investigation

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<sup>22</sup> Kaplan, D M Intermittent Pentosuria and Glycosuria, New York M J **84** 233, 1906

<sup>23</sup> d'Amato, L Su di un caso di calcolosi pancreatica con glicosuria e pentosuria, Riv crit di clin med **3** 513, 1902

<sup>24</sup> Zlataroff, A Ueber eine neue Art von Glykosurie Glukosomethylpentosurie, Ztschr f physiol Chem **97**.28, 1916

<sup>25</sup> Rosenbloom, J Report of a Case of Diabetes Mellitus Complicated by Occasional Pentosuria and Lactosuria, J A M A **64** 508 (Feb 6) 1915

<sup>26</sup> Blatherwick, N R Personal communication to the author

# CLINICAL EXPERIENCE WITH MIXTURES OF PROTAMINE ZINC AND UNMODIFIED INSULINS

## A PRELIMINARY REPORT

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All physicians who treat diabetes mellitus have long been interested in the perfecting of some type of delayed action insulin which would adequately control the level of sugar in the blood when injected once in each twenty-four hours. It was hoped that protamine zinc insulin, introduced in 1936 by Hagedorn and his associates<sup>1</sup> would be the answer to the problem of a depot of insulin. However, further experience with this type of insulin revealed that a single injection in each twenty-four hours was incapable of giving satisfactory control of the blood sugar in many cases of severe diabetes. In such cases it was often not possible to give sufficient protamine zinc insulin to control postprandial hyperglycemia during the day without producing nocturnal insulin reactions. Consequently, most authors have agreed that for satisfactory control of severe diabetes mellitus protamine zinc insulin must be supplemented by unmodified insulin<sup>2</sup>. In this scheme of treatment, the protamine zinc insulin is said to supply the patient's basal requirements, that is, the requirements for his endogenous carbohydrate metabolism<sup>3</sup>. Unmodified insulin is given during the day to supply the additional need arising from the ingestion of food (exogenous requirement).

The exact time and the manner of the administration of supplementary unmodified insulin have not been generally agreed on. Some authorities<sup>4</sup> prefer that the unmodified insulin be given in a separate injection. However, the convenience to the patient of a single injection each day has led to recommendation by several authors that the two insulins be injected together.

The use of such mixtures was first proposed by Lawrence and Aitken,<sup>5</sup> in 1938. In 1939 Lawrence<sup>6</sup> outlined a method of mixing the two types in the same syringe. Included in his report are the results of a series of determinations of

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1 Hagedorn, H C, Jensen, B N, Krarup, N B, and Wodstrup, I. Protamine Insulinate, J A M A **106** 177-180 (Jan 18) 1936

2 Peck, F B. Therapeutic Application of the Various Insulins, South Med & Surg **103** 539-545 (Oct) 1941

3 Martin, H, Drury, D R, and Strouse, S. Basal Insulin Requirement in Diabetes Mellitus, Arch Int Med **66** 78-92 (July) 1940. Ricketts, H T. The Constancy of Action of Protamine Zinc Insulin, Am J M Sc **201** 51-59 (Jan) 1941

4 Wauchope, G M. Zinc Protamine Insulin and Soluble Insulin Interaction in Combined Doses, Lancet **1** 962-966 (May 25) 1940. Masters, T D. The Uses of the Newer Insulins, Illinois M J **78** 319-323 (Oct) 1940. Smith, B, and Grishaw, W H. Survey of Diabetes. Statistical Data and Control Comparisons with Various Insulins, Arch Int Med **66** 465-477 (Aug) 1940

5 Lawrence, R D, and Aitken, R S. Discussion on the Value of Zinc Protamine Insulin in Treatment, Proc Roy Soc Med **31** 1217-1218 (Aug) 1938

6 Lawrence, R D. Zinc Protamine-Insulin in Diabetes. Treatment by One Daily Injection, Brit M J **1** 1077-1080 (May 27) 1939

the blood sugar of diabetic patients made at definite intervals after the injection of various mixtures. However, he did not hazard an opinion as to how much of the unmodified insulin entered into combination with the excess of protamine. In commercial preparations of protamine zinc insulin, the excess of protamine has been variously estimated to be from 40 to 50 per cent. More extensive studies of the effect on the level of sugar in the blood have been made by Wauchope,<sup>4</sup> Ulrich<sup>7</sup> and Colwell.<sup>8</sup>

Wauchope pointed out that the effect of a combination of the two types of insulin was modified not only by the degree of their mixing but also by the relative proportions in which they were mixed, the total number of units injected, the final hydrogen ion concentration of the mixture and the reaction of the patient's tissues to the mixture. Although he agreed that injecting the two insulins together would give adequate control of the blood sugar for the next twenty-four hours, he stated that in his experience larger total doses of insulin were required when the two were given together than when they were given separately.

Ulrich studied the effect on blood sugar of administering various mixtures of protamine zinc and unmodified insulins to diabetic patients who were either fasting or eating their usual diets, at various intervals after the injections. He concluded that in such a mixture the unmodified insulin was precipitated along with the protamine since a hypoglycemic effect was not obtained when the mixture was centrifuged and the supernatant fluid injected into a patient known to be insulin sensitive. However, since the injection of the mixture resulted in a much more rapid hypoglycemic effect than did the injection of the same total dose of protamine zinc insulin alone, he expressed the belief that the unmodified insulin had not entered into chemical combination with the excess of protamine to form protamine insulinate. He suggested that the hydrogen ion concentration of the acid solution of unmodified insulin was changed by the alkaline solution of protamine zinc insulin to near the isoelectric point of insulin, then the unmodified insulin precipitated along with the protamine zinc insulin. In his experience the injection of the mixtures of protamine zinc and unmodified insulin resulted in satisfactory control of the level of blood sugar. A mixture of 3 parts of the unmodified insulin with 2 parts of the protamine zinc insulin was, he reported, an optimal mixture.

Extensive experiments with the injection of mixtures of protamine zinc and unmodified insulins are at present being carried out by Colwell, of Evanston, Ill. In a personal communication to one of us (E. H. R.) he stated that mixtures of this type had effects on the blood sugar curves of diabetic patients which were intermediate between those of the two components of the mixtures. In his experience, satisfactory results were obtained when the mixture contained as much as 4 parts of unmodified insulin to each part of protamine zinc insulin. He raised the question whether or not these mixtures might have undergone a change due to the altered hydrogen ion concentration of the solution with formation of a new compound which had a different physiologic activity, possibly similar to that of solutions of soluble protamine insulin or globin insulin.

At the Mayo Clinic we have been using mixtures of the two types of insulin in the routine treatment of severe diabetes since Lawrence<sup>6</sup> published his observations. In our experience this method of treatment has proved satisfactory for a large proportion of diabetic patients. However, there are still cases in which adequate control of the diabetes has been difficult or impossible with this method.

7 Ulrich, H. Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulin, *Ann Int Med* **14** 1166-1179 (Jan) 1941.

8 Colwell, A. R. Personal communication to the authors.

Furthermore, the question of which scheme of adjusting the amounts of each type of insulin gives the best results has not yet been answered. Masters stated "The so-called 'educated guess' based on experience in handling a large diabetic service remains the most satisfactory solution to the problem of gauging insulin dosage." An "educated guess," however, can hardly solve the problem of the diabetic patient who daily must adjust his own dosage of insulin, nor can it serve the needs of the average physician who lacks the opportunity of becoming so adept. Since variations in the daily requirement of insulin in severe diabetes necessitate daily adjustment in dosage, we have attempted to devise some scheme for making these adjustments. None of the methods of adjustment which we have employed thus far has been entirely satisfactory. For this reason we have studied the effects on diabetic patients of injecting various mixtures. Our investigations were carried out along the lines suggested by the work of Ulrich, Wauchope and Colwell. In this paper we wish to make a preliminary report of our work, which as yet is limited.

#### CONDITIONS OF STUDY AND PROCEDURES

The scheme of treatment used in our studies conformed as closely as possible to that employed in the usual care of diabetic patients at the clinic.

Our observations were made on 2 young women who had severe diabetes. Each had been under our observation throughout most of the course of her illness. Neither presented any complications which might interfere with the interpretation of our results, and both consented to the special study.

These patients were admitted to our nutritional ward for a preliminary period of stabilization, lasting ten days in each instance, before the study was begun. They were placed on standard diabetic diets, the caloric content of which was determined by calculations based on their age, height and ideal weight from tables which had been prepared by Boothby and Berkson.<sup>9</sup> The total daily allowance of food was divided into three meals of ordinary size, given at 8 a. m., 12 noon and 5 p. m., and one small feeding at 9 p. m. All of the food was weighed and prepared in the kitchen attached to the nutritional ward. The mineral content of each of the menus was known, and since these were rotated every three days, we believe that a reasonably constant mineral balance was maintained throughout the period of observation. The sodium chloride content of the diet was maintained at approximately 10 Gm daily, 5 or 6 Gm was contained in the food, and 4 or 5 Gm was given in a saltcellar to be added to the food as the patient desired. The total daily allowance of fluid was kept at 2,000 cc. The intake and the output of fluids in each case were measured each day, and a satisfactory fluid balance was found to be maintained.

The patients were ambulatory and were encouraged to engage in activities similar to those which they ordinarily performed at home. No medication other than insulin was given to either patient. Both remained in good spirits and excellent health throughout the period of observation.

Each day four single specimens of urine, obtained at 6 a. m., 11 a. m., 4 p. m. and 9 p. m., were analyzed qualitatively for sugar. In addition, each twenty-four hour specimen of urine was analyzed quantitatively for dextrose.

The mixtures of the two types of insulin were given half an hour before breakfast unless otherwise specified. The site of injection was changed each day. In drawing the insulin into the syringe, the unmodified insulin was taken in first, the protamine zinc insulin second. No particular attempt was made to mix the two insulins more thoroughly since it had not been our custom to do so in the past. Both types of insulin were used in the strength of 80 units per 1 cc. Since we used protamine zinc insulin from one lot for the whole study, we believe that the excess of protamine per unit of protamine zinc insulin in each mixture injected was approximately the same amount.

The dosage of insulin was adjusted during the preliminary period of observation in accordance with the rules outlined by Wilder.<sup>10</sup> Briefly, the dose of protamine zinc insulin was determined by an analysis of the urine made at 6 a. m. and the dose of unmodified insulin by an analysis made at 4 p. m. In each instance the dose of insulin was reduced when the reaction was 0 or grade 1+, was left the same when the reaction was grade 2+

<sup>9</sup> Boothby, W. M., and Berkson, J., cited by Wilder.<sup>10</sup>

<sup>10</sup> Wilder, R. M. *A Primer for Diabetic Patients*, ed 7, Philadelphia, W. B. Saunders Company, 1941.

and was increased after a reaction of grade 3 to 4+. No supplementary doses of insulin were given during the day. By this method we were able to arrive at a reasonably constant total dose of insulin which would be satisfactory for each patient. The figure for this dose having been obtained in each instance, it was possible arbitrarily to give the total dose in various mixtures representing a series of ratios of protamine zinc to unmodified insulin. Changes in these ratios were made every fourth day. The concentrations of blood sugar were determined in series on the third day of administration of each ratio. By placing this interval between each series of determinations we hoped to eliminate the influence on the level of the blood sugar of the protamine zinc insulin in the preceding dosage.

The method used in determining the level of the blood sugar on the days selected was as follows. Samples of capillary blood were taken half an hour preceding and one hour following each meal, and twenty-four hours after the injection of the mixture being studied. The dextrose content of the blood samples was determined by a micromethod. We have plotted the blood sugar levels obtained in this manner as curves in order to compare the results of all observations. Such a series will be referred to hereafter in this paper as a "blood sugar curve." This is to be distinguished from the usual curve obtained from the sugar tolerance test. Occasionally, in order to determine the average trend of the blood sugar level from several series of determinations, the values which form the basis of several curves have been averaged and plotted. These average values and the resultant curve will be referred to as the "mean" curve hereafter in this paper.

RATIO OF PROTAMINE ZINC INSULIN TO UNMODIFIED  
INSULIN USED IN 100 CASES

As a preliminary to consideration of the results obtained in our special study of 2 patients, we should like to include the results of a study of the dosage of

*Ratio of Protamine Zinc Insulin to Unmodified Insulin in the Total Dose of  
One Hundred Diabetic Patients*

Ratio *	Total Daily Dose							
	Less Than 20 Units		20-40 Units		40 or More Units		Entire Group	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
1-1	23	65.7	4	8.5			27	27
1-2	3	8.6	14	29.8	8	44.4	25	25
1-3			13	27.6	5	27.8	18	18
1-4			2	4.3			2	2
1-5			1	2.1			1	1
1-6			1	2.1			1	1
2-3	9	25.7	10	21.3	2	11.1	21	21
2-5			2	4.3	2	11.1	4	4
4-5					1	5.6	1	1
Total	35	100	47	100	18	100	100	100

\* Ratio of protamine zinc insulin to unmodified insulin

insulin in 100 cases of diabetes taken at random from the files. The disease in these cases was severe enough to require the administration of a mixture of both types of insulin. We were interested in discovering which ratio or ratios were most often arrived at in these cases when satisfactory control was obtained.

The results of this preliminary study are summarized in the accompanying table. If a total of less than 20 units of insulin was required daily, the commonest ratio observed was that of 1 part protamine zinc insulin to 1 part of unmodified insulin, if a total of 20 to 40 units was required, the most frequently encountered ratios were 1-2, 1-3 and 2-3, if a total of 40 or more units was required, ratios of protamine zinc insulin to unmodified insulin of 1-2 and 1-3 were most common. If then the entire series was taken together as a group, with the amounts of insulin required in each case being disregarded, the numbers of cases in which the diabetes was controlled satisfactorily with mixtures representing ratios of the protamine zinc insulin to unmodified insulin of 1-1, 1-2, 1-3 and 2-3 were approximately equal.

Thus it appears that there is no optimal ratio of the two types of insulin which is automatically arrived at by the method of adjustment of insulin dosage which we have been using. However, ratios of the protamine zinc insulin to the unmodified insulin of 1/2, 1/3 or 2/3 apparently come nearest to an ideal mixture.

### RESULTS

**CASE 1**—The patient was an unmarried woman aged 19 years, whose diabetes had developed in 1932 after an attack of acute pharyngitis. A paternal aunt and uncle and one brother also had diabetes. The patient herself had been under a dietary and insulin regimen since the onset of her diabetes but had been repeatedly in trouble because of frequent acute infectious diseases and frequent lapses in the management of her diabetes. On four occasions, the last one in 1940, she had been in severe acidosis, twice the acidosis was so severe that it produced coma.

At the time of her admission to the nutritional ward, in November 1941, she was 62 inches (152 cm) in height and weighed 139 pounds (63 kg). General physical examination, examination of the ocular fundi and routine laboratory studies, including a roentgen study of the thorax and a flocculation test of the blood, revealed nothing of significance.

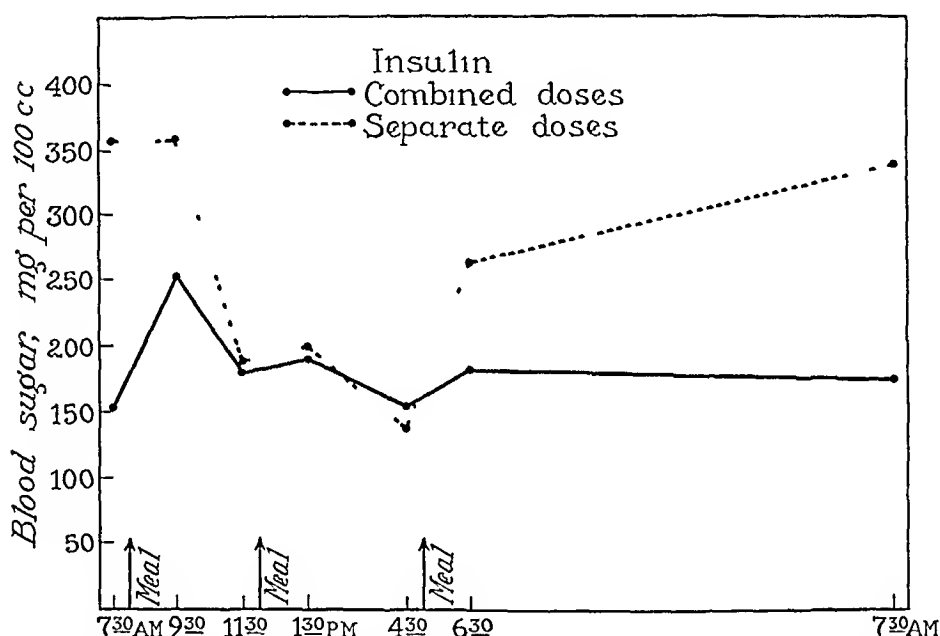


Chart 1 (case 1) —Comparison of mean curves obtained on administering the two types of insulin in one syringe (combined dose) and on administering each type at a separate site (separate dose).

Because the patient weighed 21 pounds (9.5 kg) more than her ideal weight, a diet of only 40 per cent more than her basal caloric requirements was prescribed. On this diet her weight was maintained throughout the period of observations. During the period of preliminary study it was determined that her daily requirement of insulin was approximately 80 units.

Fifteen blood sugar curves were obtained in this case. During the first part of our study we obtained blood sugar curves after the administration of mixtures of protamine zinc insulin and unmodified insulin in various ratios as follows: 1/5, 1/4, 1/3, 1/2, 1/1, 2/5 and 2/3, in the order named. The patient then was allowed a few days of rest. In the second part of the study, blood sugar curves were obtained after the administration of mixtures of the protamine zinc insulin to unmodified insulin in the ratios of 1/0 (protamine zinc alone), 1/1, 1/2, 1/3 and 1/4, in that order. In the third part of our study we obtained blood sugar curves after the injection of protamine zinc and unmodified insulins in ratios of 1/1, 1/2 and 1/3 in separate sites. Finally a blood sugar curve was obtained after the administration of a suitable mixture one hour instead of half an hour before breakfast.

The "mean" curve calculated from the values for blood sugar in the various blood sugar curves obtained after the injection of mixtures of protamine zinc insulin and unmodified insulin in the ratios of 1/2, 1/3, 1/4, 2/3 and 2/5 is shown in chart 1. This curve shows the essential features of the pattern of blood sugar which resulted from the injection of mixtures representing what we may call "intermediate ratios." With one exception, satisfactory control of

the level of sugar in the blood was maintained throughout the twenty-four hours by the injection of these mixtures, that is, postprandial hyperglycemia was not excessive, and the fasting blood sugar levels were within the range of adequate control. The one exception to the good control was after the morning meal. All of the curves show this midmorning hyperglycemia, which presumably was due to a lag in the blood sugar-lowering effect of the mixtures. This finding coincides with the observation frequently made in cases in which the injection of the mixture fails to prevent hyperglycemia and heavy glycosuria at 11 a. m., even though both were under good control at 6 a. m. and 4 p. m. Ulrich observed this same phenomenon. Evidently, mixing the two insulins resulted in a lessening of the rapidity with which the unmodified insulin begins to exert its hypoglycemic effect. However, we do not believe that this slowing of the immediate hypoglycemic effect of the insulin in the mixtures constitutes a serious objection to their use, since the glycemic levels throughout most of the twenty-four hour period following the injection of the mixtures were within reasonable limits and the total excretion of dextrose was usually less than 20 Gm.

For comparison we have included in chart 1 a similar "mean" curve representing the mean values of blood sugar from three series of determinations obtained after the injection of the

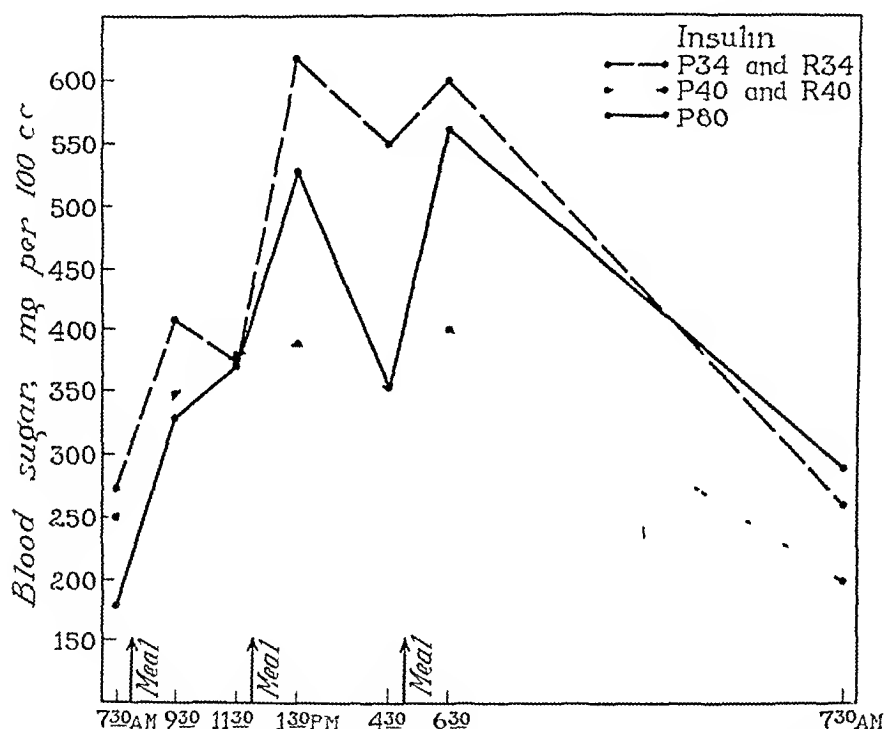


Chart 2 (case 1) — Comparison of blood sugar curves obtained after the administration of a total dose of protamine zinc insulin alone and mixtures of equal parts of the two types of insulin

two insulins in separate sites. The ratios of the amounts of protamine zinc insulin and unmodified insulin represented in these curves were 1:1, 1:2 and 1:3. The second "mean" curve shows striking differences from the first "mean" curve, representing the effect of injection of the mixtures. It may be seen that the injection of the unmodified insulin in a separate site not only prevented the midmorning occurrence of hyperglycemia but also produced a rapid fall in the level of sugar in the blood shortly thereafter. However, during the latter part of the twenty-four hour curve the level of the blood sugar rose considerably higher than it did in the comparable period which followed the administration of the mixtures. This finding probably indicates that in the mixtures some of the unmodified insulin entered into combination with the excess protamine to form protamine insulin, thus the mixture contained relatively more protamine zinc insulin than would a similar total dose of insulin in which the protamine and unmodified components were given separately.

A curve of blood sugar obtained following the injection of the total dose as protamine zinc insulin alone is compared graphically in chart 2 with two curves obtained after the injection of mixtures of equal parts of protamine zinc and unmodified insulins. All three curves were similar, that is, with protamine zinc insulin alone or with a mixture of protamine zinc insulin

and unmodified insulin in the ratio of 1:1, control of the level of sugar in the blood was adequate in the fasting state but inadequate when the subject was allowed to eat. Marked postprandial hyperglycemia is characteristic of the effects of both types of insulin. Because of this similarity we believe that in mixtures of equal parts of protamine zinc and unmodified insulins the latter type of insulin must have entered for the most part into combination with the excess protamine, so that little unmodified insulin remains. It is obvious, therefore, that the patient gains little by the use of mixtures of equal parts of protamine zinc and unmodified insulins over the result from the use of the same total dose of protamine zinc insulin alone.

On comparison of the curve obtained after the injection of equal parts of the two types of insulin in a mixture and a curve obtained after the administration of a mixture of 1 part of protamine zinc insulin and 5 parts of unmodified insulin a marked difference is found (chart 3). Whereas little immediate hypoglycemic or unmodified insulin effect is evident in the first curve, in the second curve the rapid decrease in the level of sugar in the blood occurs after the administration of insulin. This result would be expected after the injection of a relatively large dose of unmodified insulin. We have interpreted this result to indicate that in a mixture in which the amount of unmodified insulin is much larger than the amount of protamine zinc insulin, only a small proportion of the unmodified insulin enters into combination with the extra protamine, an excess of unmodified insulin, therefore, is left to produce a marked immediate hypoglycemic effect. It should be noted, however, that despite the excess of unmodi-

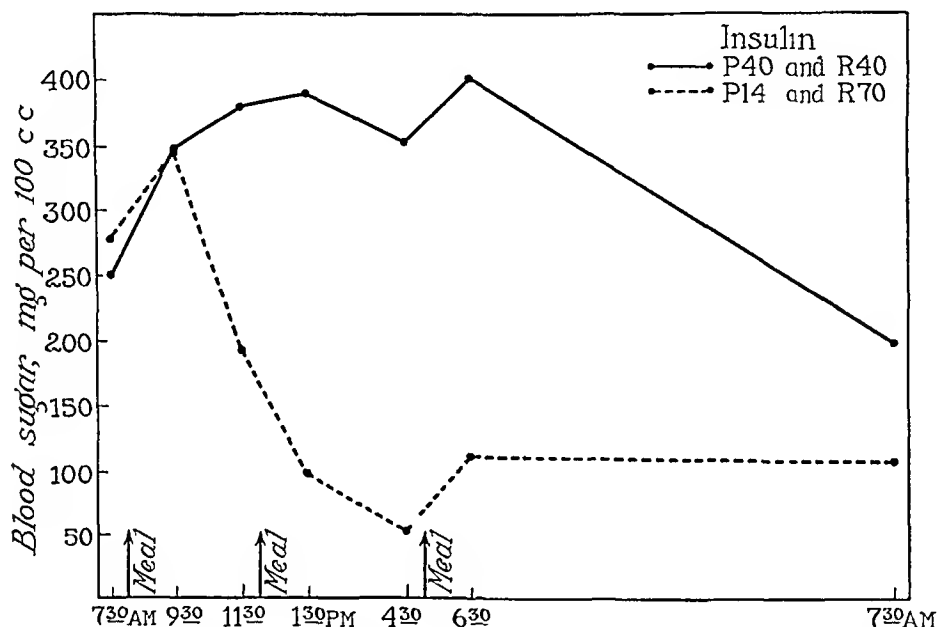


Chart 3 (case 1) —Comparison of curves obtained following injection of mixtures of insulin in which the ratio of protamine zinc insulin to unmodified insulin was either 1:1 or 1:5

fied insulin in this mixture the characteristic "lag" in hypoglycemic effect in the midmorning period is still evident. Perhaps the presence of the protamine modifies the activity of the unmodified insulin even though the two insulins in combination did not.

The "mean" curve representing the results of the injection of the two types in the various intermediate ratios half an hour before breakfast is compared with the results obtained after the administration of a suitable mixture one hour before breakfast in chart 4. We were interested in determining whether or not a more satisfactory control of the level of blood sugar could be obtained by giving the insulin long enough before the morning meal to eliminate the midmorning lag in blood sugar-lowering effect. As may be seen in chart 4, injecting the mixture earlier in the morning did eliminate the midmorning hyperglycemia, presumably because sufficient time elapsed between the injection of the insulin and the ingestion of food to permit the hypoglycemic effect of the insulin to begin before the ingestion of food started to elevate the blood sugar. However, in this case the remainder of the blood sugar curve obtained following this earlier injection did not show as smooth control of the glycemic level as did curves obtained following the injection of the insulin half an hour before breakfast.

**CASE 2**—Our second subject was an unmarried woman 21 years of age, whose diabetes had begun abruptly one year before her entry into the nutritional ward. During that time her diabetes had been well controlled by a standard diabetic diet and one daily injection of a mixture of protamine zinc and unmodified insulins.



On admission to the nutritional ward in January 1942 the patient weighed 122 pounds (55.5 Kg) and was 66 inches (167 cm) in height. General physical examination, examination of the ocular fundi and routine laboratory studies, including a roentgen study of the thorax and a flocculation test of the blood, revealed nothing of significance. Because her weight was approximately normal, a diet of 50 per cent more than her basal calorie requirements was

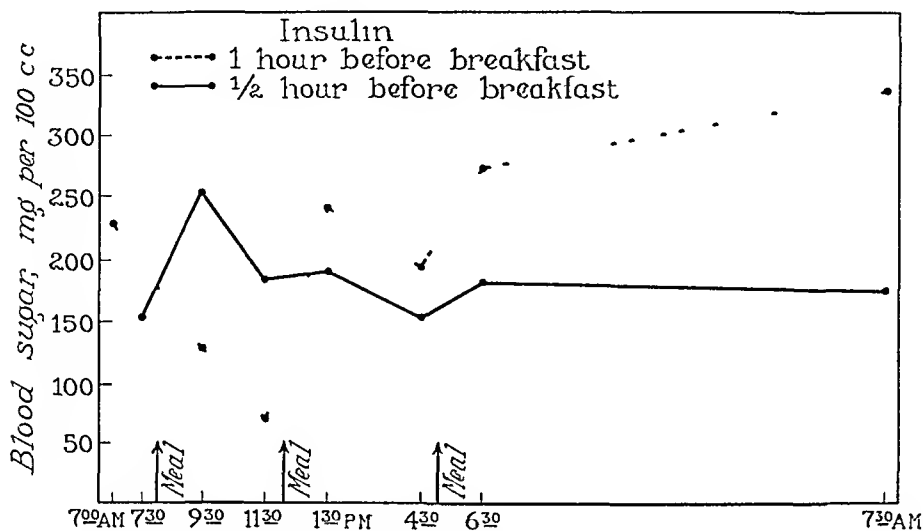


Chart 4 (case 1) — Comparison of blood sugar curves obtained after injecting mixtures of the two types of insulin one hour and half an hour before breakfast

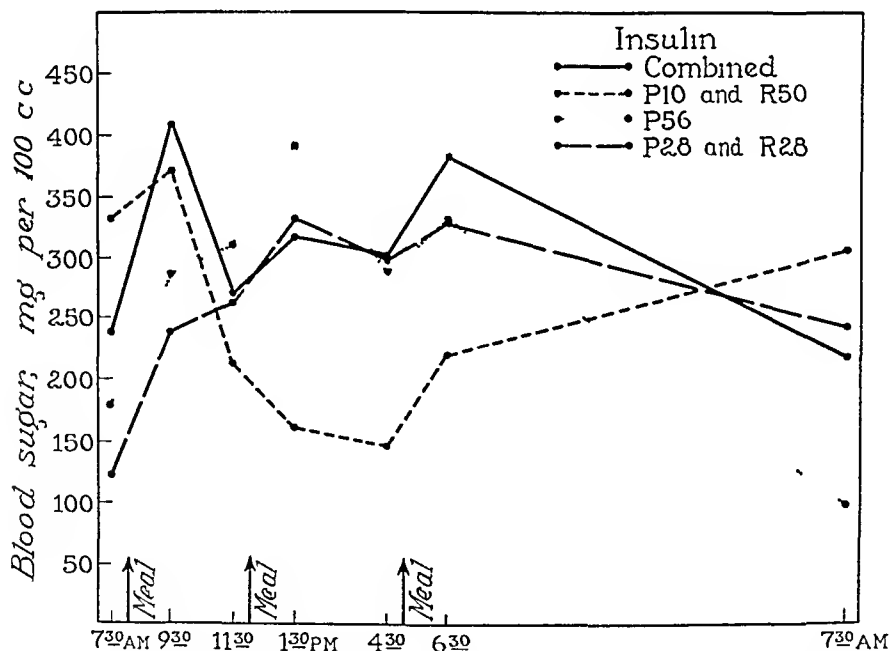


Chart 5 (case 2) — Six blood sugar curves. The curve labeled "combined" is the mean curve, the method of obtaining the mean curve and descriptions of the other curves are given in the text.

prescribed. During the first ten days of observation it was found that her daily insulin requirement was approximately 70 units.

Six blood sugar curves were obtained in this case. These are all represented in chart 2. The first curve is a "mean" curve calculated from three individual curves obtained after the injection of insulin mixtures in which the ratios of the protamine zinc insulin to the unmodified insulin were 1/2, 1/3 and 1/4, respectively. In nearly all respects, this mean curve of the level of sugar in the blood, in chart 2, is similar to the mean curve which we have already

presented for case 1. In this case, as in case 1, control of the level of sugar in the blood by the injection of various mixtures of the two types of insulin was good throughout most of the twenty-four hour period, with the exception of the period between the morning and noon meals.

The curves with dosage ratios of 1:1 and 1:0 in chart 5 indicate the similarity between an injection of a mixture of equal parts of protamine zinc and unmodified insulin and a single injection of protamine zinc insulin alone in effect on the blood sugar level throughout the twenty-four hours following their injection.

The curve in chart 5 with the ratio of 1:5 for the two types of insulin indicates that the injection of a mixture of insulins in this ratio produced the same effect on the level of sugar in the blood in case 2 as it did in case 1. This mixture of 5 parts of unmodified insulin to 1 part of protamine zinc insulin resulted in a predominantly rapid hypoglycemic or unmodified insulin effect.

#### COMMENT

Although our studies have been limited, we believe that our results so far warrant at least certain tentative deductions.

On the whole, mixtures of protamine zinc insulin and unmodified insulin have been shown to be capable of controlling to a satisfactory degree the levels of sugar in the blood of diabetic patients throughout the twenty-four hour period following their injection. With the exception of the period after breakfast, postprandial elevations of the blood sugar were minimal. We feel that the lag in the immediate hypoglycemic effect of the mixtures does not constitute a serious objection to their use in cases of severe diabetes.

We have not been able to demonstrate that any one ratio of the protamine zinc insulin to unmodified insulin gave an optimal effect in the 2 cases studied, nor were we able to find an ideal mixture in a study of ratios such as seemed to obtain in the 100 cases of diabetes in which the two insulins were given in a single injection. However, ratios of protamine zinc insulin to unmodified insulin which lay between the two extremes of 1:1 and 1:5 gave the most satisfactory control in most instances, that is, mixtures in which the ratios of protamine zinc insulin to unmodified insulin were 1:2, 1:3, 1:4, 2:3 and 2:5 were capable of adequate control of the blood sugar during the twenty-four hours after their injection. The use of a mixture of equal parts of the two insulins resulted in blood sugar curves very similar to those obtained when the dose consisted of protamine zinc insulin alone. In such a mixture, we believe, most of the unmodified insulin was in combination with the excess protamine. On the other hand, a mixture of 1 part of protamine zinc insulin to 5 parts of unmodified insulin resulted in a marked immediate hypoglycemic effect such as might be expected to follow the injection of a large dose of unmodified insulin alone. Evidently in such a mixture most of the unmodified insulin remained uncombined.

We did not find that injection of the two types of insulins at separate sites gave as satisfactory control of the blood sugar level in the subsequent twenty-four hours as their injection together. Following their injection in separate sites, a marked immediate hypoglycemic effect was obtained, but smooth control of the level of the blood sugar during the remainder of the day and especially overnight did not result.

Finally, we tried to eliminate the midmorning lag in hypoglycemic effect of the mixtures of the two insulins by injection of the dose of insulin one hour instead of half an hour before breakfast. Although this method eliminated the lag, it did not result in smoother control of the blood sugar during the remainder of the twenty-four hours.

# IN SITU EFFECTS OF ANTACIDS IN DUODENAL ULCER

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An attempt at neutralization of the acid gastric juice is one of the basic purposes common to most of the conventional methods of treatment of peptic ulcer. In order to secure more effective neutralization it has become rather universal practice to employ any of several antacid medications, all of which have been extolled for their peculiar virtues and each of which has its own group of proponents. Alkaline substances continue to succeed one another in favor, largely as their several advocates are able to demonstrate a greater degree of reduction or a more prolonged reduction of acidity in the stomach.

The concerted efforts directed toward modification of gastric acidity are natural outgrowths of the emphasis which has been laid on the acid factor in ulcer. It is surprising, however, that so much attention has been given to gastric acidity when the vast majority of the ulcers encountered clinically are situated not in the stomach but in the first part of the duodenum. If acidity is really an important factor in duodenal ulcer, then the acidity and neutralizing ability at the actual site of the ulcer and not those in the stomach should be ascertained. Similarly, if antacid therapy is really beneficial in the management of duodenal ulcer because of reduction of acidity, then the changes produced by antacids in the acidity and neutralizing ability at the actual site of the ulcer rather than in the stomach should be determined.

Our purpose in this study was to observe the simultaneous effects of some of the commonly employed antacids on the reaction and neutralizing ability in the pyloric antrum and in the duodenal bulb in a group of patients with chronic duodenal ulcer. In our opinion, antacid therapy for duodenal ulcer can be properly evaluated from the standpoint of changes in acidity only by observations made directly at the locale of the ulcer—only by observations, in other words, of the in situ effects.

## MATERIAL

A group of 17 patients (13 men and 4 women) ranging in age from 26 to 59 years were selected from the outpatient gastrointestinal disease clinic of the Jefferson Hospital. All of them either were complaining at the time of symptoms attributable to an ulcer or had been symptom free for a very short period. A number had had previous episodes of bleeding, and

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all of them had definite roentgenologic evidence of a nonobstructive duodenal ulcer. In the few instances in which it had been done, gastroscopic examination revealed an essentially normal gastric mucosa.

#### METHOD

Each patient appeared in the morning before breakfast and after a twelve hour fast. A specially constructed double lumen tube was employed also and a procedure followed which allowed more or less constant fluoroscopic control and also permitted the making of roentgenograms providing proof of the position of the tube<sup>1</sup>. Material was simultaneously aspirated from the pyloric antrum and from the duodenal cap at intervals of ten minutes. Specimens were collected for one-half hour while the subject was in the fasting state and for two hours after his ingestion of an Ewald meal, consisting of two pieces of dry toast or stale bread and 250 cc of tap water. Immediately after the withdrawal of the specimens at the thirty minute postprandial interval each patient was given by mouth either 15 cc of a preparation of aluminum hydroxide gel<sup>2</sup> plus 15 cc of tap water or 10 grams (0.6 Gm) of sodium bicarbonate and 30 grains (2 Gm) of calcium carbonate (Sippy powder) plus 15 cc of tap water.

The  $p_H$  of each specimen was determined at once by means of a Leeds-Northrup  $p_H$  indicator, which uses a glass electrode. After filtration the free and the total acidity of each specimen were estimated, with Topfer's reagent and phenolphthalein as the respective color indicators<sup>3</sup>. For each duodenal specimen, in addition, there was determined what was called the excess neutralizing ability<sup>4</sup>. This is expressed as the amount of tenth-normal hydrochloric acid necessary to lower the  $p_H$  to the point at which Topfer's reagent indicated a positive reaction for free acid<sup>3</sup>.

The patients were divided into two groups. One patient served as a subject in both groups, making a total of 9 patients in each. On one group (7 men and 2 women) 19 experiments were performed with aluminum hydroxide gel, while on the other 7 men and 2 women 19 experiments were performed with Sippy powder. The 38 experiments so performed involved 3,703 separate determinations. The latter included 1,003 readings of  $p_H$ , 1,084 estimations of free acid, 1,084 estimations of total acidity and 532 determinations of excess neutralizing ability of the duodenal contents. In expressing the results, the 4 readings made with the subject in the fasting state were averaged to give a single value.

#### RESULTS

In the accompanying figures (1 to 8 inclusive) there are shown the curves obtained by plotting the average values observed with the use of the antacids aluminum hydroxide gel and Sippy powder. The curves of the controls, which are presented for comparison, represent the average values obtained for a group of patients with duodenal ulcer who had been fed the same Ewald meal and studied in a similar fashion but had not received any antacid<sup>5</sup>. Included among the controls are 12 of the 17 patients who comprise the series receiving an antacid, an attempt purposely being made to obtain studies on as many of the control patients as possible in order to insure a fairer comparison. Of such patients, a few who had had active symptoms when the control observations were made were symptom free at the time of the experiments with the antacid. Inasmuch as our primary interest lay in observing the effects of orally administered alkaline

1 Berk, J. E., Rehfuess, M. E., and Thomas, J. E. A Method for the Simultaneous Aspiration of the Contents of the Stomach and the First Part of the Duodenum, *J. A. M. A.* **119** 259 (May 16) 1942.

2 The preparation used was amphojel (John Wyeth & Brother, Inc.)

3 Berk, J. E., Thomas, J. E., and Rehfuess, M. E. Limitations in the Use of Color Indicator in Gastric Analysis, *Am. J. Digest. Dis.* **9** 106, 1942.

4 Berk, J. E., Thomas, J. E., and Rehfuess, M. E. (a) The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal, *Am. J. Physiol.* **136** 157, 1942, (b) footnote 3.

5 Berk, J. E., Rehfuess, M. E., and Thomas, J. E. The Effect of Ulcer on the Reaction and Neutralizing Ability in the Duodenal Bulb, *Arch. Int. Med.* **70** 959 (Dec.) 1942.

substances on gastric and duodenal acidity, we did not feel that the subsidence of active symptoms in these patients impaired the validity of the comparisons of acidities determined before and after ingestion of an antacid, because it has been fairly well established that no essential change occurs in the degree of gastric acidity with healing of a duodenal ulcer.<sup>6</sup> The close adherence of the control and the antacid curves to each other in the period prior to the administration of the respective antacids (figs 1, 3, 5 and 7) may be taken as support for this assumption.

*Acidity in  $p_H$  Units* (figs 1 and 2)—Stomach The two antacids caused decreases in average hydrogen ion concentration of equal duration, although the magnitude of the decrease was greater with Sippy powder than with aluminum

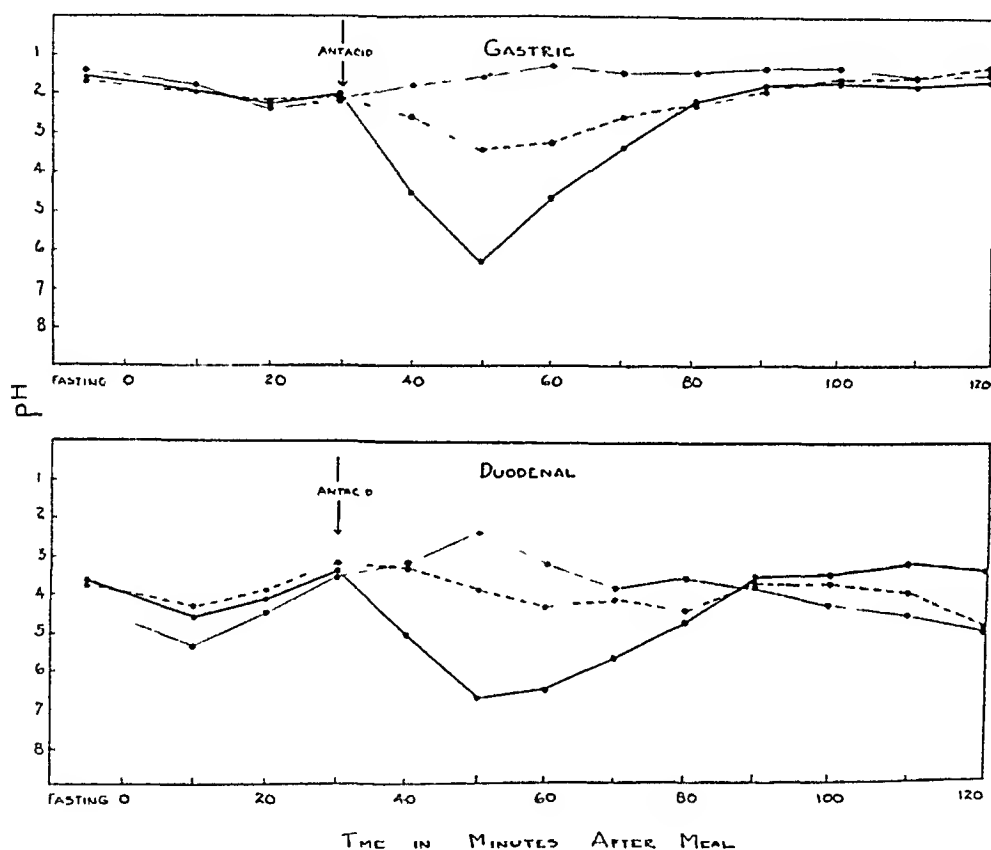


Fig 1—Average acidity in  $p_H$  units of samples collected simultaneously from just above and just below the pylorus before and after the administration of an antacid. The dotted line represents values for patients who received aluminum hydroxide gel, the heavy unbroken line, for patients who received Sippy powder, and the light unbroken line, for patients who did not receive an antacid (controls).

6 (a) Bloomfield, A. L., and French, L. R. Basal Gastric Secretion in Cases of Peptic Ulcer. Relation of Acidity to Healing of Ulcer, *J Clin Investigation* **17** 667, 1938. (b) Bockus, H. L., Glassmire, C., and Bank, J. Fractional Gastric Analysis in Two Hundred Cases of Duodenal Ulcer, *Am J Surg* **12** 6, 1931. (c) Brown, C. F. G., and Dolkart, R. E. Gastric Acid During Recurrences and Remissions of Duodenal Ulcer, *Arch Int Med* **60** 680 (Oct) 1937. (d) Hurst, A. F., and Venables, J. F. The True Incidence of Hyperchlorhydria in Gastric and Duodenal Ulcer, *Guy's Hosp Rep* **79** 249, 1929. (e) Sandweiss, D. J., Sugarman, M. H., Friedman, M. H. F., Saltzstein, H. C., and Farbman, A. A. The Effect of Urine Extracts on Peptic Ulcer. An Experimental and Clinical Study, *Am J Digest Dis* **8** 371, 1941.

hydroxide gel Neither antacid, however, was eminently successful in causing any prolonged elevation of average  $p_H$  above 3.5, the value which we had adopted as the critical one for free acid.<sup>3</sup> With Sippy powder the forty, fifty and sixty minute determinations were in excess of  $p_H$  3.5 and hence negative for free acid, with aluminum hydroxide gel only the fifty minute determination exceeded this value (fig 1)

The contrast in effects on gastric hydrogen ion concentration was more favorably seen in the frequency distribution of the observations made in the period after administration of the antacid (fig 2) Not one of the control values exceeded  $p_H$  3.5, in fact all of them were  $p_H$  3.0 or less. On the other hand, 10.1 per cent of the readings following ingestion of aluminum hydroxide gel and 31.1 per cent of those following ingestion of Sippy powder were greater than  $p_H$  3.5

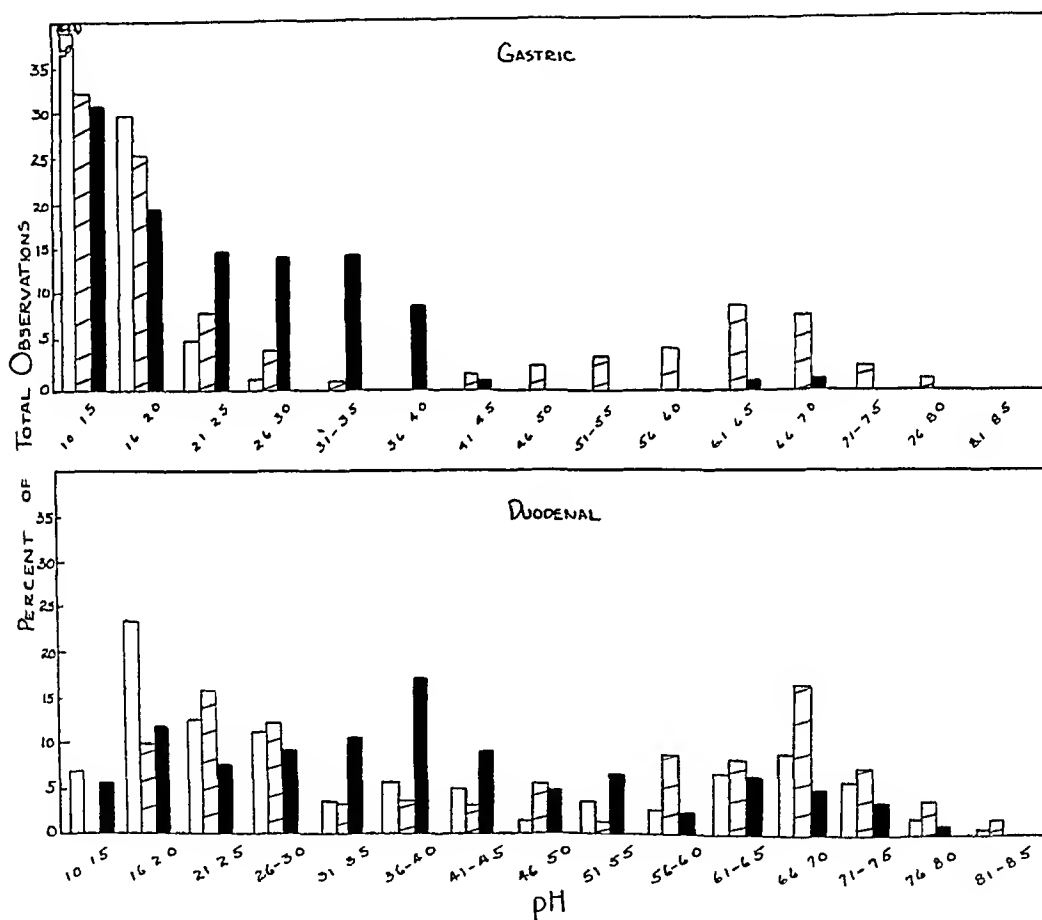


Fig 2—Frequency distribution of observations of  $p_H$  of samples collected simultaneously from just above and just below the pylorus after the administration of an antacid and in control experiments during the corresponding period. Values for patients receiving aluminum hydroxide gel are represented by solid bars, for patients receiving Sippy powder by bars with cross hatching, and for patients not receiving an antacid, by white bars

No secondary rise in gastric hydrogen ion concentration occurred with either antacid during the period of observation

**Duodenum** The control patients displayed an ineffective neutralizing ability in their duodenal bulbs at the forty, fifty and sixty minute readings (inability to neutralize gastric free acid as evidenced by an inability to maintain a  $p_H$  of 3.5 or greater). Aluminum hydroxide gel corrected this defect to some extent, in that only the forty minute determination showed ineffective neutralization, otherwise, the

general effect on duodenal  $p_H$  was slight. Sippy powder acted more promptly and produced a higher peak level of average duodenal  $p_H$ , this was largely offset, however, by a secondary increase in hydrogen ion concentration, which was so great that ineffective neutralization ( $p_H$  of 3.5 or less) characterized the last half-hour of the observation period (fig 1).

The general ineffectiveness of these antacids in the duodenum is well shown in the frequency distribution of the observations (fig 2). The contents of the first part of the duodenum in the specially noted postantacid phase contained free acid ( $p_H$  3.5 or less) in 57.7 per cent of the control observations and in 40.6 per cent of the observations following use of Sippy powder and in 43.4 per cent of those following use of aluminum hydroxide gel—differences of questionable significance.

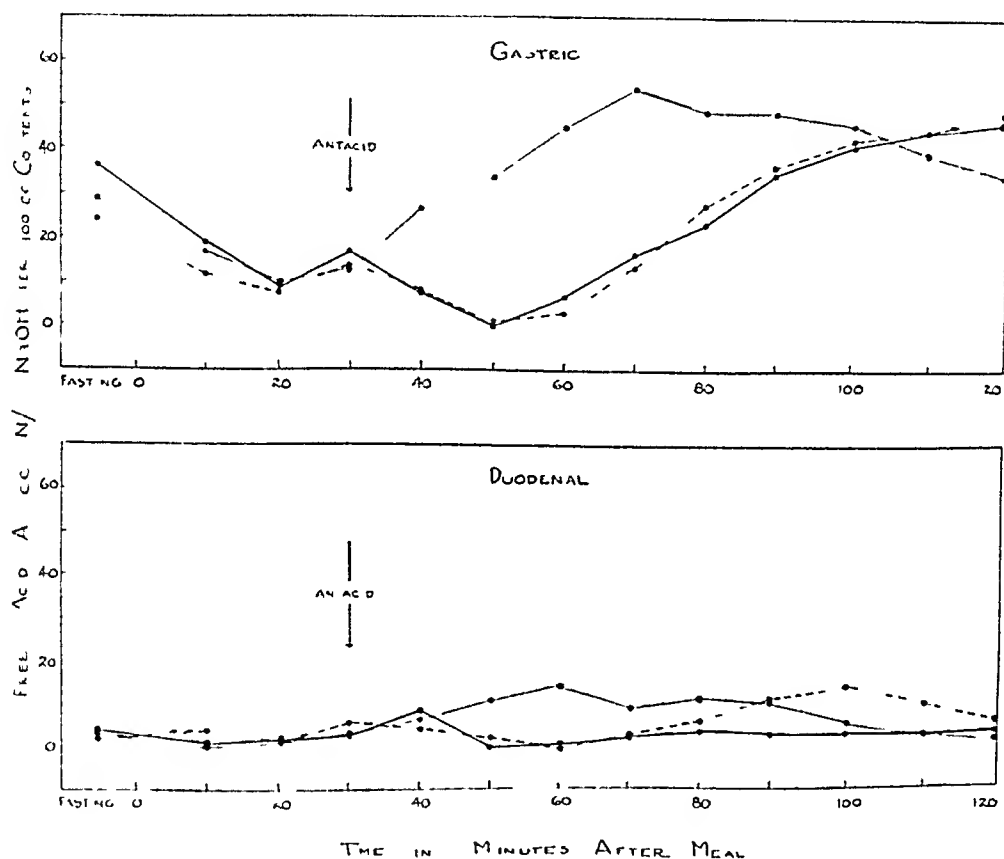


Fig 3—Average free acid as determined on samples collected simultaneously from just above and just below the pylorus before and after the administration of an antacid. See the legend for figure 1 for an explanation of the curves.

The graphic average curves of  $p_H$  in the stomach and duodenum following administration of an antacid bore a rough resemblance to each other. An exact parallelism, however, was not discerned, and in the last half-hour of the observation period the duodenal curves were distinctly of different pattern than their respective gastric homologues (fig 1). Of special note, too, was the exhibition of a secondary rise in duodenal acidity with Sippy powder in the absence of such a phenomenon in the stomach. These discrepancies are worthy of emphasis, for they illustrate an inability to accept observations of gastric behavior as accurate indexes of the corresponding effects on acidity in the first part of the duodenum.

*Free Acid* (figs 3 and 4)—Stomach Even though a complete achlorhydria was obtained at a single interval reading only (fifty minutes), a diminution of the average values of free acid in the gastric juice was obtained. This was of about equal magnitude and duration with the two antacids (fig 3). All of the control specimens contained some titratable free acid, whereas 37 per cent of the specimens studied after ingestion of Sippy powder and 35.3 per cent of those examined after ingestion of aluminum hydroxide gel were colorimetrically negative for free acid. Both these percentages are greater than was indicated by the corresponding gastric  $p_H$  values (fig 2). This is not surprising, however, for, as we have pointed out,<sup>3</sup> with our technic the filtration and dilution of the specimens preparatory to colorimetric titration result in a number of false negative readings for free acid. Since

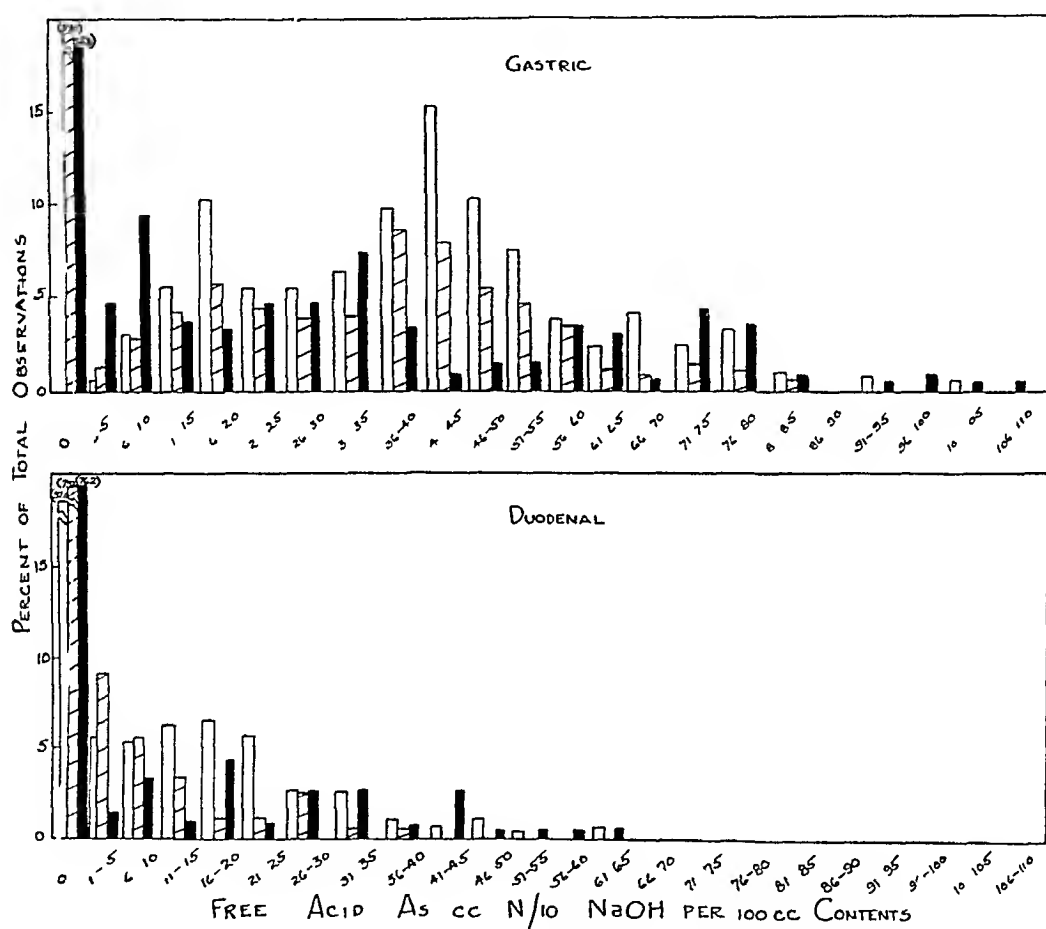


Fig 4—Frequency distribution of observations of free acid as determined on samples collected simultaneously from just above and just below the pylorus after the administration of an antacid and in control experiments during the corresponding period. See the legend for figure 2 for an explanation of the figure.

our average end point with Topfer's reagent was close to  $p_H$  3.5,<sup>3</sup> all specimens whose  $p_H$  in the unfiltered, undiluted state is 3.5 or less must be considered as containing free acid. Interpreted in the light of this criterion, the  $p_H$  values afford the more accurate index of the true incidence of achlorhydria.

A mild secondary rise in average gastric free acid was seen following use of each antacid (fig 3), a phenomenon which was not observed in the behavior of the average gastric  $p_H$ .

The graphic curve of average gastric free acid after ingestion of aluminum hydroxide gel (fig 3) adopted a definitely different pattern than that shown by the



corresponding curve of average duodenal  $p_H$  (fig 1) It may be said, then, that this measure of acidity in the stomach, as far as aluminum hydroxide gel is concerned at any rate, cannot be taken to indicate with any surety the coexistent effective acidity ( $p_H$ ) in the duodenal bulb

**Duodenum** Despite its salutary effect on gastric free acid, aluminum hydroxide gel failed to display an ability to reduce duodenal free acid in a similar fashion Not only was it less effective in this respect than was Sippy powder, but it produced a secondary rise in duodenal acidity which did not occur after use of Sippy powder (fig 3) A more favorable comparison appears when the percentage of samples taken after ingestion of an antacid that are colorimetrically negative for free acid is considered, 76.2 per cent of the observations after use of aluminum

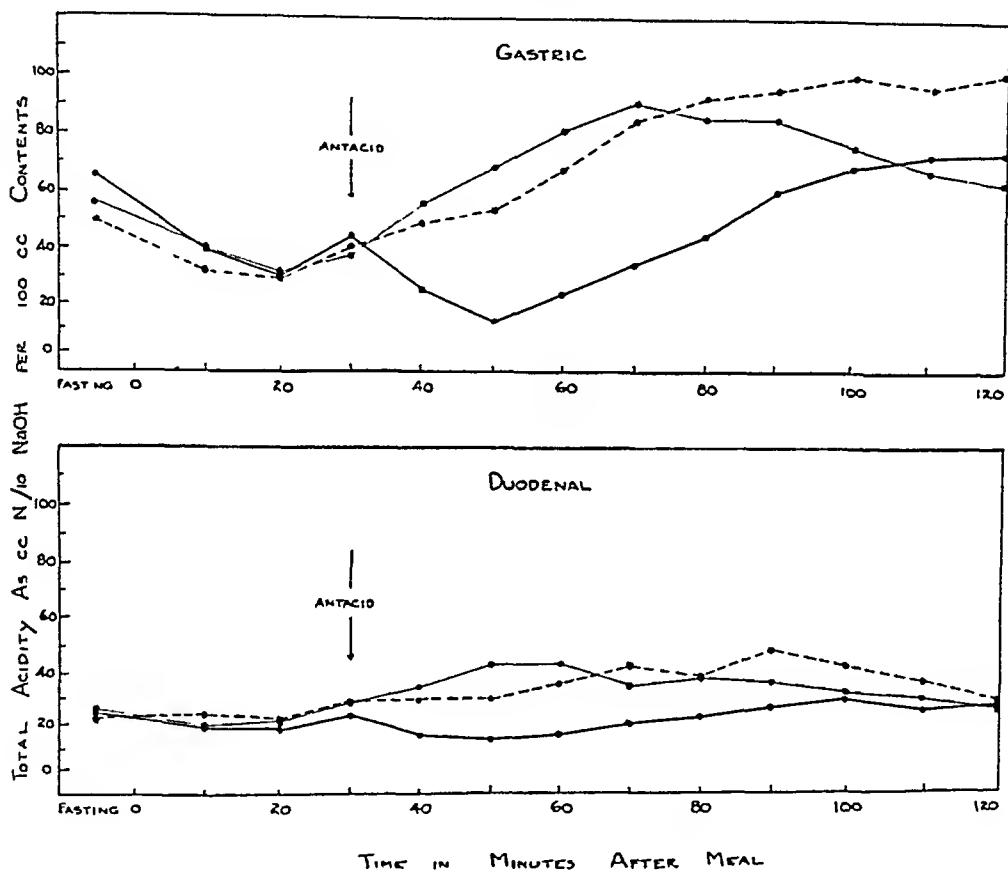


Fig 5—Average total acidity of samples collected simultaneously from just above and just below the pylorus before and after the administration of an antacid See the legend for figure 1

hydroxide gel and 75.5 per cent of those after use of Sippy powder showed no free acid, in contradistinction to 57.7 per cent of the control observations (fig 4) These percentages, however, are again greater than the corresponding ones based on determinations of duodenal  $p_H$  and must be interpreted in the light of the error which is known to exist in the method of colorimetric titration

**Total Acidity** (figs 5 and 6)—**Stomach** Aluminum hydroxide gel not only appeared to be devoid of any beneficial effect on average gastric total acidity but, paradoxically, caused a greater concentration of titratable acidity than that which obtained without use of any antacid (fig 5) This situation, however, is more apparent than real, for it is to be remembered that the sodium hydroxide used in

the titrimetric procedure combined not only with the hydrochloric acid of the gastric contents but with the aluminum chloride formed from the interaction of the aluminum hydroxide of the gel and the hydrochloric acid of the chyme. Therefore, determinations of total acidity following the administration of aluminum hydroxide gel give no indication of its efficacy as an antacid.

Sippy powder exhibited an effect on gastric average total acidity similar to that on free acid (fig 3). The effect reached its peak rapidly, progressively lessened and finally reached the control level after about an hour. The comparatively lesser action of this antacid on the  $p_H$  in the duodenal cap (fig 1) bespeaks the fact that measurement of gastric total acidity also fails as a reliable index of the actual changes in effective duodenal acidity ( $p_H$ ) which may follow the use of an antacid.

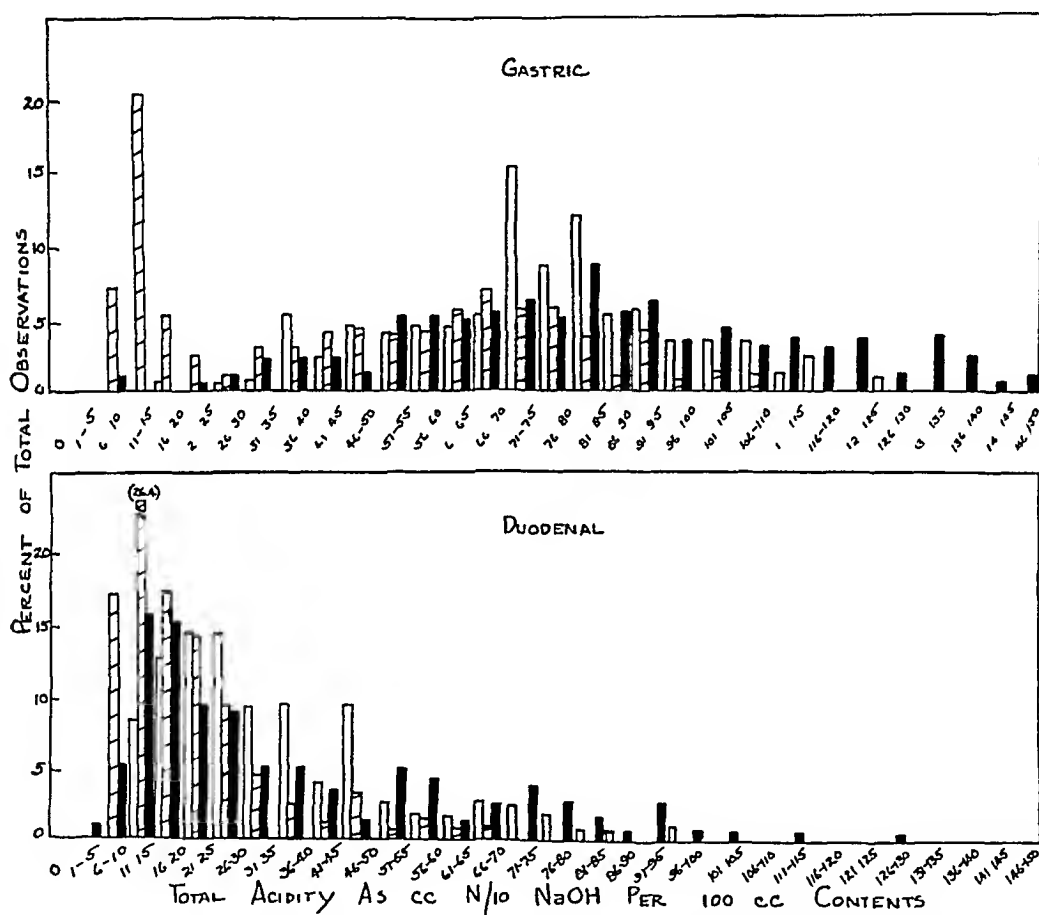


Fig 6—Frequency distribution of observations of total acidity of samples collected simultaneously from just above and just below the pylorus after the administration of an antacid and in control experiments during the corresponding period. See the legend for figure 2.

**Duodenum** As in the stomach and for the reasons stated in that connection, aluminum hydroxide gel appeared to contribute little if at all to lowering the average total acidity of the contents of the duodenal cap (fig 5). Sippy powder, on the other hand, effected a reduction of total acidity in this area.

*Excess Neutralizing Ability of the Duodenal Contents* (figs 7 and 8) — Excess neutralizing ability has been defined<sup>4</sup> as a measure of the reserve capacity possessed by the contents of the duodenal bulb to neutralize, buffer and dilute the chyme received from the stomach above that necessary to offset the free acid content. Aluminum hydroxide gel, it will be seen in figure 7, was essentially non-

contributory to this reserve ability Sippy powder, on the contrary, greatly enhanced the excess neutralizing ability of the duodenal contents. The latter action may be attributed, in all probability, to the free sodium bicarbonate carried over into the duodenum along with the chyme emptying from the stomach. As with the other observed effects of Sippy powder, the enhancement was of relatively brief duration and was offset in the terminal phase by a diminution of the reserve capacity below that of the control series.

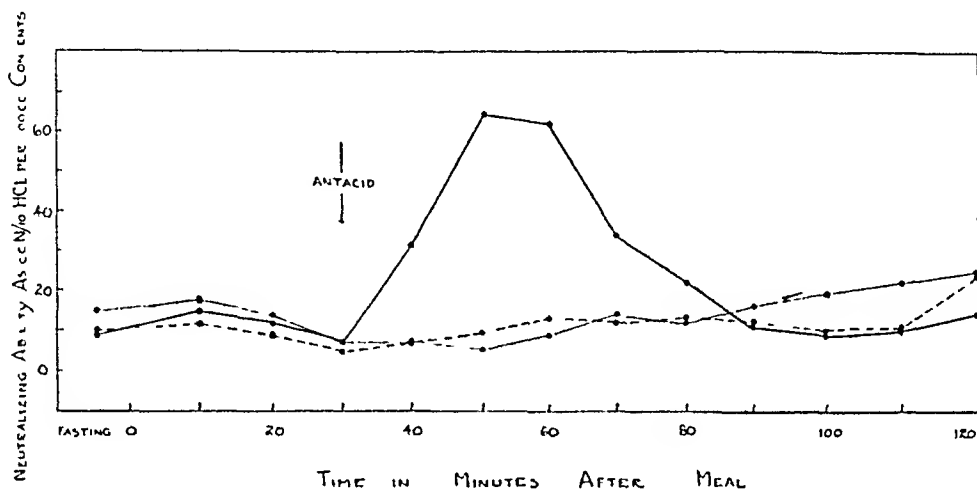


Fig 7—Average excess neutralizing ability of the duodenal contents before and after the administration of an antacid. See the legend for figure 2.

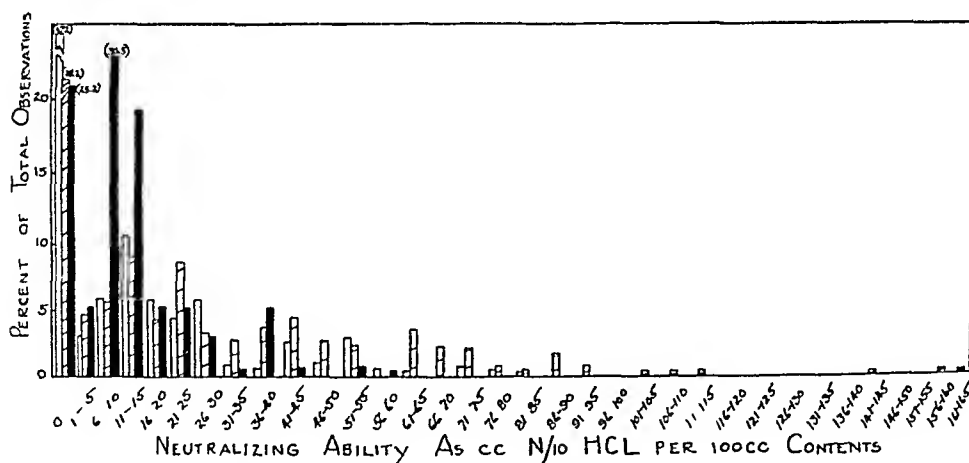


Fig 8—Frequency distribution of observations of excess neutralizing ability of the duodenal contents after the administration of an antacid and in control experiments during the corresponding period. See the legend for figure 2.

#### COMMENT

In presenting the results, attention repeatedly has been called to the disparity between the observed simultaneous gastric and duodenal effects of the two antacids. It was noted that salutary effects on gastric acidity were commonly associated with comparative ineffectiveness as regards reduction of duodenal acidity and that undesirable secondary rises in acidity occurred in the duodenum in the absence of

such phenomena in the stomach. It may be concluded, therefore, that the *in situ* effects of antacids on duodenal acidity in patients with duodenal ulcer cannot be predicted from their behavior in the stomach, just as their intragastric effects, in turn, cannot be predicted from their potential *in vitro* neutralizing capacity.<sup>7</sup>

The effective acidity in the first part of the duodenum, the harboring nest of most clinical ulcers, is determined by the hydrogen ion concentration of its contents, which in turn finds expression in the  $p_H$  value. A lack of close correlation was pointed out between the values of the several measures of gastric acidity and the coexistent  $p_H$  in the duodenal cap. It is important to emphasize the fact that, generally speaking, after the use of an antacid none of the customary indexes of gastric acidity may be taken to indicate reliably the coexistent effective acidity ( $p_H$ ) in the duodenal bulb.

The results indicate that the oral administration of an antacid in the commonly employed therapeutic doses enhances the neutralizing ability of the contents of the first part of the duodenum. It is to be stressed, however, that the reduction of intraduodenal acidity was not great, lasted only a comparatively short period of time and was followed in the instance of Sippy powder by a rebound increase in duodenal hydrogen ion concentration. The use of larger amounts and/or more frequent doses of antacid might well overcome these shortcomings, but the patient with an ulcer would then become subjected to the added risk of such complications as alkalosis,<sup>8</sup> impaired renal function with kidney stone formation,<sup>9</sup> constipation,<sup>10</sup> fecal impaction,<sup>8</sup> intestinal obstruction<sup>11</sup> and interference with absorption of inorganic phosphates.<sup>12</sup> We have found that duodenal acidity is greatly affected by the type of food undergoing digestion<sup>13</sup> and that in dogs fats (cream, olive oil and

7 (a) Breuhaus, H. C., and Eyerly, J. B. Antacids: Their Effect by Titration and Within the Human Stomach, *Ann Int Med* **14** 2285, 1941. (b) Eyerly, J. B. Comparative  $p_H$  Values Within the Stomach, Pylorus, and Duodenum in Antacid Therapy, *Am J Digest Dis* **7** 431, 1940.

8 (a) Dick, C. F., and Eisele, C. W. The Treatment of Peptic Ulcer Without Alkalis, *J A M A* **118** 38 (Jan 3) 1942. (b) Eisele, C. W. Changes in the Acid-Base Balance During Alkali Treatment for Peptic Ulcer, *Arch Int Med* **63** 1048 (June) 1939. (c) Hardt, L. L., and Rivers, A. B. Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, *ibid* **31** 171 (Feb) 1923. (d) Kirsner, J. B., and Palmer, W. L. The Role of Chlorides in Alkalosis Following the Administration of Calcium Carbonate, *J A M A* **116** 384 (Feb 1) 1941.

9 Eisele, C. W. Role of Alkali Therapy for Peptic Ulcer in Formation of Urinary Calculi, *J A M A* **114** 2363 (June 15) 1940.

10 Kraemer, M. The Use of Hydrated Magnesium Trisilicate in Peptic Ulcer, *Am J Digest Dis* **5** 422, 1938. McIntosh, J. F., and Sutherland, C. G. Use of Colloidal Aluminum Hydroxide in Treatment of Peptic Ulcer, *Canad M A J* **42** 140, 1940.

11 Havens, W. P. Intestinal Obstruction Caused by Colloidal Aluminum Hydroxide, *J A M A* **113** 1564 (Oct 21) 1939.

12 Fauley, G. B., Freeman, S., Ivy, A. C., Atkinson, A. J., and Wigodsky, H. S. Aluminum Phosphate in the Therapy of Peptic Ulcer. Effect of Aluminum Hydroxide on Phosphate Absorption, *Arch Int Med* **67** 563 (March) 1941. Freeman, S., and Freeman, W. M. The Interference in the Absorption of Inorganic Phosphorus by Aluminum Hydroxide. Its Use in Children with Chronic Renal Insufficiency, *Am J Physiol* **133**:281, 1941. Street, H. R., and Barlow, O. W. The Relative Effects of Aluminum Hydroxide and Aluminum Sulfate on the Absorption of Dietary Phosphorus by the Rat, *ibid* **133** 465, 1941.

13 Berk, J. E., Thomas, J. E., and Rehfuess, M. E. (a) The Effect of Gastric Hypersecretion on the Reaction and Neutralizing Ability of the Contents of the First Part of the Duodenum in Normal Dogs, *Am J Digest Dis* **9** 297, 1942. (b) The Effect of a Cream Meal on the Acidity and Neutralizing Ability of the Contents of the Duodenal Bulb in Normal Dogs, *Am J Physiol* **136** 285, 1942. (c) footnote 4a. (d) Thomas, J. E. The Maximal Acidity of the Intestinal Contents During Digestion, *Am J Digest Dis* **7** 195, 1940. (e) Thomas, J. E., and Crider, J. O. The Effect of Fat on the  $p_H$  of the Contents of the Duodenum, *Am J Physiol* **114** 603, 1936.

beef fat) exhibit a striking depressant effect on duodenal acidity which is maintained for a considerable time<sup>13c,e</sup> True, the amounts of fat we employed were greatly in excess of the amounts which are commonly given to patients, yet there is evidence that small doses of fat (olive oil and cod liver oil) depress secretion in the gastric pouch in dogs effectively and over long periods<sup>14</sup> One might therefore expect a similarly effective action in the duodenum from small doses of such palatable fats as cream Certainly the use of fats is devoid of the inconvenience, expense and complications attendant on the frequent administration of antacid medications Should a duodenal antacid effect prove desirable in the management of a patient with ulcer, the preferential use of dietary measures, especially of fatty foodstuffs, is to be strongly considered

Accumulated clinical experience leaves no doubt that antacid medications exert a beneficial action in the treatment of patients with duodenal ulcer Basically the reason for their use and the enthusiasm with which they have been applied in the therapy of ulcer stem from the importance which has been assigned to the acid factor in this disease and to the assumed need for its modification The literature, however, is replete with reports denying any remarkable or sustained neutralizing effects in the stomach following ingestion of an antacid<sup>15</sup> Our results indicate, further, absence of any pronounced or prolonged neutralization at the site of the duodenal ulcer when a single therapeutic dose of an antacid is given to a patient with ulcer after an Ewald meal In our own experience as well as in that of others,<sup>8a</sup> most patients with uncomplicated duodenal ulcer respond equally satisfactorily on a regimen devoid of antacids as when antacids are employed The disappearance of abdominal pain after the ingestion of an antacid may alone warrant its employment, in spite of the demonstrated lack of any correlation with the changes in gastric acidity<sup>15k</sup>

The most arresting evidence striking at the very foundation of the popular theory of antacid therapy is the demonstration that definite healing of experimental (Mann-Williamson) ulcers in dogs and distinct symptomatic improvement in patients with duodenal ulcer may occur with the use of extracts from the urine of pregnant and of normal women without any decrease in the gastric secretory response to stimuli<sup>6e</sup> It is difficult to escape the conclusion, therefore, that what-

14 Komarov, O, and Komarov, S A The Effect of Olive Oil and Cod-Liver Oil on Gastric Secretion in the Dog, *Canad M A J* **43** 129, 1940

15 (a) Adams, W L, Einsel, I H, and Meyers, V C Aluminum Hydroxide as an Antacid in Peptic Ulcer, *Am J Digest Dis* **3** 112, 1936 (b) Boyd, T E The Influence of Alkalies on the Secretion and Composition of Gastric Juice I The Effect of the Prolonged Administration of Sodium Bicarbonate and Calcium Carbonate, *Am J Physiol* **71** 455, 1925 (c) Breuhaus and Eyerly<sup>7a</sup> (d) Brown and Dolkart<sup>6c</sup> (e) Crohn, B B Studies in Fractional Estimation of Gastric Contents II Effects of Antacid Medication on Gastric Acidity and Secretion, *Am J M Sc* **155** 801, 1918 (f) Degener, M Untersuchungen über den Einfluss von Alkalien auf Motilität und Sekretion des Magens mittels der fraktionierten Ausheberung, *München med Wchnschr* **75** 1838, 1928 (g) Eyerly<sup>7b</sup> (h) Ivy, A C, Terry, L, Fauley, G B, and Bradley, W B The Effect of Administration of Aluminum Preparations on the Secretory Activity and Gastric Acidity of the Normal Stomach, *Am J Digest Dis* **3** 879, 1936 (i) Kirsner, J B A Further Study of the Effect of Various Antacids on the Hydrogen Ion Concentration of the Gastric Contents, *ibid* **8** 53, 1941 (j) Kirsner, J B, and Palmer, W L The Effect of Various Antacids on the Hydrogen Ion Concentration of the Gastric Contents, *ibid* **7** 85, 1940 (k) Steigmann, F, and Fantus, B Acidity Modification Therapy in Peptic Ulcer, *ibid* **7** 197, 1940 (l) Wosika, P H, and Emery, E S, Jr The Effectiveness of the Sippy Regimen in Neutralizing the Gastric Juice of Patients if the Amount of Alkali Is Not Varied, *Ann Int Med* **9** 1070, 1936 (m) Wylkie, D The Influence of Certain Antacids on the Acidity of Human Gastric Juice, with Special Reference to Magnesium Trisilicate, *Edinburgh M J* **47** 336, 1940

ever is the contribution of antacids to the management of patients with duodenal ulcer, their beneficial clinical action must be attributed to something more than their slight efficaciousness in reducing acidity at the site of the ulcer.

A comparative evaluation of the relative merits of the two antacids employed was not a primary purpose in this study. In many respects Sippy powder showed a neutralizing ability superior to that of aluminum hydroxide gel, but this seeming excellence requires qualification, and the suggested superiority must be accepted with caution. Aluminum hydroxide gel is known to be a slow acting antacid. With our method of study the withdrawal of small amounts of gastric and duodenal contents at ten minute intervals, all of which must have contained some of the administered antacid, would affect the end results of a slower acting antacid to a much greater degree than it would such a rapid acting one as Sippy powder. Despite a prompt and more rapid decrease in duodenal hydrogen ion concentration after ingestion of Sippy powder, there followed a secondary rise which tended to offset the apparent advantage of Sippy powder over aluminum hydroxide gel.

#### SUMMARY AND CONCLUSIONS

The in situ effects of antacids on duodenal acidity in patients with duodenal ulcer cannot be predicted from their behavior in the stomach.

After the ingestion of an antacid by a patient with duodenal ulcer none of the customary indexes of gastric acidity may be taken to indicate reliably the coexistent effective acidity ( $p_H$ ) in the duodenal bulb.

Oral administration of an antacid in the usual therapeutic dose to a patient with duodenal ulcer does reduce the acidity of the contents of the first part of the duodenum. The reduction of intraduodenal acidity, however, is neither great nor long lasting and may be followed by a rebound increase.

The beneficial clinical action of antacids in the management of patients with duodenal ulcer must be attributed to something more than their slight efficaciousness in reducing acidity at the site of the ulcer.

Dr B B Vincent Lyon gave us permission to use the patients and facilities of the gastrointestinal disease clinic, and Drs Melvin Dillman and Karl Kornblum performed the roentgen studies on each subject.

# SYMPTOMS AND INCIDENCE OF ANEMIA IN HERNIA AT THE ESOPHAGEAL HIATUS

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Instances of true hernia at the esophageal hiatus were recorded not infrequently in the literature of the early part of this century, but, with improvement in roentgenographic technic during the past twenty years and with accumulating interest in the subject, the rather high incidence of the condition has been recognized. The incidence in relation to the number of gastrointestinal roentgen studies made by several authors has varied from 0.75 to as high as 2.9 per cent of the series.<sup>1</sup> This must not be interpreted as evidence that such a high percentage of the general population has hiatal hernia, because the majority of the roentgen examinations were made for persons with complaints referable to the gastrointestinal tract.

Åkerlund<sup>2</sup> in 1926 cited 60 cases recorded in the literature up to that time and reported 24 of his own. Harrington<sup>3</sup> reported 680 cases seen at the Mayo Clinic between Jan 1, 1908 and Dec 31, 1939. The first of these cases was diagnosed in 1908, at the time of an operation, and in 1921 the first diagnosis by roentgen examination was recorded.

Three varieties of so-called hiatal hernia have been described by Åkerlund:<sup>2</sup> that associated with a congenitally short esophagus, a paraesophageal type and a gastroesophageal type. In the type occurring with a congenitally short esophagus a part or all of the stomach is permanently within the thorax (partial or complete thoracic stomach). Failure of the esophagus to reach a proper length during development has made it impossible for the stomach to develop in the normal position, which is entirely within the peritoneal cavity. In the paraesophageal type of hiatal hernia the esophagus is of normal length and its lower end remains situated below the level of the diaphragm in its normal position whereas the fundus of the stomach is herniated through the esophageal hiatus so that it lies within the posterior mediastinum. In the gastroesophageal type the esophagus is of normal length, but the lower end is carried up above the level of the diaphragm with the herniated stomach, which lies in the posterior mediastinum.

Harrington<sup>3</sup> expressed the opinion that in some instances the stomach is drawn into the thorax by cicatricial contraction of a healed ulcer at the lower end of the esophagus, the resulting condition being confused with hernia of the

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From the Medical Clinic of the Peter Bent Brigham Hospital

1 (a) Ritvo, M. Hernia of the Stomach Through the Esophageal Orifice of the Diaphragm, *J A M A* **94** 15 (Jan 4) 1930. (b) Eisen, D. Esophageal Hiatus Hernia, *Canad M A J* **39** 207 (Sept) 1938. (c) Rigler, L G, and Eneboe, J B. The Incidence of Hiatus Hernia in Pregnant Women and Its Significance, *J Thoracic Surg* **4** 262 (Feb) 1935. (d) Levy, M D, and Duggan, L B. Hiatus Hernia of the Stomach, *South M J* **34** 351 (April) 1941.

2 Åkerlund, A. Hernia diaphragmatica hiatus oesophagei vom anatomischen und röntgenologischen Gesichtspunkt, *Acta radiol* **6** 3, 1926.

3 Harrington, S W. Diagnosis and Treatment of Various Types of Diaphragmatic Hernia, *Am J Surg* **50** 381 (Nov) 1940.

congenital variety Dunhill<sup>4</sup> described in place of the third type what he termed "hernia diaphragmatica transversa" In this condition the esophagus is of normal length but the anatomic hiatus is replaced by a large defect due to nondevelopment of the crura of the diaphragm

The presence of hiatal hernia is still commonly first suspected only after its demonstration by the roentgenologist The symptoms presented by the patient are most likely to be ascribed to some disturbance such as peptic ulcer or carcinoma or disease of the gallbladder or of the organs within the thorax, the symptoms of which are more familiar to the physician Attention may be directed away from the hernia as the cause of the symptoms because of the coexistence of one of those conditions and the hernia The common failure of the physician to include hiatal hernia in the differential diagnosis is probably the result of variation in the symptom complex and of lack of knowledge of what the various symptoms are Harrington<sup>3</sup> has referred to hiatal hernia as the "masquerader of the upper abdomen" because of the change in the symptom complex as the size and the condition of the hernia change with age

The objects of the study reported here are two (1) to determine those symptoms occurring in patients with herniation which may lead one to suspect the diagnosis, (2) to record the frequency of anemia in patients with hiatal hernia and its importance as a diagnostic aid

#### MATERIAL STUDIED

The data recorded are based on 72 case histories of patients with hiatal hernia, taken from the wards and outpatient department of the Peter Bent Brigham Hospital and the private records of one of us (W P M) Hernia of the type occurring with a congenitally short esophagus was present in 7 instances Although there is some question as to whether or not this is true herniation because of the fact that the end of the esophagus and the stomach have never been in their normal position, these cases are most conveniently included for discussion with those of true hernia The remaining 65 cases of hiatal hernia have not been further classified, because the data available did not warrant differentiation into smaller subgroups It seemed to us likely that the distinction between the paraesophageal and the gastroesophageal type is largely dependent on the degree of herniation at the time the roentgen examination is made The position of the lower end of the esophagus and the size of the portion of the stomach herniated into the posterior mediastinum depend largely on the condition of the patient at the time of examination

*Sex*—Of the 72 patients, 11 were men and 61 women Eleven women were unmarried, 12 were married but had borne no children, and the marital status of 1 is unknown The remaining 37 women had borne one or more children

It has been generally recognized that hiatal hernia is more common in female than in male patients, as in our series In the series of Rigler and Eneboe<sup>1c</sup> there were 15 females to 4 males These authors also called attention to the frequency with which herniation accompanies pregnancy They found roentgen evidence of hiatal hernia in 181 per cent of 116 multipara Marks<sup>5</sup> observed that herniation occurred most commonly in women who are over 40 years of age and overweight

*Age*—The 72 patients were distributed with respect to decades of life at the time the diagnosis was made as follows 30 to 39 years, 4, 40 to 49 years, 12, 50 to 59 years, 23, 60 to 69 years, 19, 70 to 79 years, 14 The youngest patient, a woman, was 33 years of age when the diagnosis was made, but the symptoms had persisted since a fall from a stone fence at the age of 20, when she landed prone with a large boulder under her abdomen The oldest patient was 78 The average age of the series was 60 years It was often difficult to determine the age at which the onset of symptoms occurred because of uncertainty as to whether these were the result of hernia or of some other ailment However, as nearly as could be determined, the average age at onset of symptoms was 57 years

4 Dunhill, T Diaphragmatic Hernia, Brit J Surg **22** 475 (Jan) 1935

5 Marks, J H Diaphragmatic Hernia and Associated Conditions, Am J Roentgenol **37** 613 (May) 1937



Harrington<sup>6</sup> found hiatal hernia to be most common in the decade between 50 and 60 years. Moersch<sup>7</sup> and also Levy and Duggan<sup>1d</sup> found the average age to be 55 years, the extremes in their series of 26 cases were 27 and 79 years. The average age of 128 patients with hiatal hernia reported by Jones<sup>8</sup> was 55 years. It is not clear whether the ages reported for these various series are those at the time of onset of symptoms or those at the time the diagnosis was made.

#### CONGENITALLY SHORT ESOPHAGUS AND THORACIC STOMACH

Bailey<sup>9</sup> was probably the first to direct attention to, and describe, a case of congenitally short esophagus with complete thoracic stomach when in 1919 he reported such a condition found during the dissection of the body of a 77 year old man. LeWald<sup>10</sup> was perhaps the first to recognize thoracic stomach by roentgen examination. In 1924 he described this condition in 2 persons, a child of 7 years and a man of 69 years. He stated that "thoracic stomach is an entity of congenital origin with development of the diaphragm below it, without structural defect." Truesdale<sup>11</sup> found reports of 20 cases of "complete thoracic stomach" and of 41 cases of "partial thoracic stomach" with a short esophagus in the literature up to 1935.

Seven of our series of patients with hiatal hernia were found to have a congenitally short esophagus. In only 1 of them was the stomach completely above the diaphragm—complete thoracic stomach. Five women and 2 men, 1 of whom also had pernicious anemia, comprise this group. A brief history of each of them is included here because of the somewhat unusual interest in this condition.

CASE 1—A 59 year old woman, single, had for eighteen months previous to examination complained of regurgitation of food recently eaten and of having several times vomited bloody material. She also complained of heartburn, gas and distention in the upper part of the abdomen, as well as of the sensation that food met an obstruction half way down, and she seemed to have difficulty in swallowing solid foods. Three months previous to her admission to the Peter Bent Brigham Hospital an ulcer of the esophagogastric junction had been demonstrated by roentgenogram. The stools showed occult blood (2 plus by the guaiac test), and she had moderately severe anemia, as shown by a red blood cell count of 3,850,000 and a hemoglobin content of 7.87 Gm. Roentgen examination showed that the esophagus ended 10 cm above the diaphragm, with an ulcer at the distal end. The fundus of the stomach was herniated through the esophageal hiatus.

CASE 2—A 53 year old woman, married, stated that three months before admission she had experienced a severe attack of asthmatic bronchitis following a cold. Since then there had been a frequently recurring cough with wheezing. During this time she also had a "squeezing hurt" substernally, not related to exertion but frequently occurring after breakfast. Three years previous to entrance she had nausea and vomiting, her condition at that time was diagnosed by roentgenogram as duodenal ulcer, and her symptoms were relieved by diet. She had diverticula of both the sigmoid and the transverse colon. No anemia was present and no occult blood was demonstrated in the feces. Roentgen examination on this admission to the hospital showed that the esophagus ended 4 cm above the diaphragm. A portion of the fundus of the stomach was herniated through the hiatus. No ulcer was seen.

CASE 3—A 60 year old woman, single, complained for a number of years of an upper abdominal pain accompanied by gas, however, the pain was intermittent in character, at times during the past six months it had disappeared for several days. When she had pain, she ate no food, drank hot water and was generally relieved. Headaches and constipation had

6 Harrington, S. W. Esophageal Hiatus Diaphragmatic Hernia, *J Thoracic Surg* 8 127 (Dec) 1938.

7 Moersch, H. J. Hiatal Hernia, *Ann Otol, Rhin & Laryng* 47 754 (Sept) 1938.

8 Jones, C. M. Hiatus Esophageal Hernia, with Special Reference to Comparison of Its Symptoms with Those of Angina Pectoris, *New England J Med* 225 963 (Dec 18) 1941.

9 Bailey, P. A Case of Thoracic Stomach, *Anat Rec* 17 107 (Oct) 1919.

10 LeWald, L. T. Thoracic Stomach. Differentiation from Eventration and Hernia of the Diaphragm, *Radiology* 3 91 (Aug) 1924.

11 Truesdale, P. E. Diaphragmatic Hernia at the Esophageal Hiatus, *New England J Med* 212 240 (Feb 7) 1935.

increased in frequency. She had moderately severe anemia, characterized by a hemoglobin content of 11.59 Gm and a red blood cell count of 3,780,000. The feces were positive for occult blood (1 plus by the guaiac test). Roentgenograms of the upper part of the gastrointestinal tract showed that the esophagus ended 5 cm above the diaphragm and that the fundus of the stomach herniated through the esophageal hiatus. Diverticulosis of the colon was demonstrated by a barium sulfate enema.

CASE 4—A 56 year old man was first seen in the outdoor department in June 1927, complaining that he had suffered from pain in the left lower quadrant of the abdomen for the past four weeks. This pain came on while he was eating and radiated to the front of the chest, where it seemed to choke him and where it seemed to cause him to regurgitate food several times after eating. Five months later he was seen again, at which time he complained of midabdominal pain which came immediately after eating and radiated up to the throat. The pain was relieved by eructation of gas. Roentgen studies at that time revealed a duodenal ulcer and a hiatal hernia. Five years later he was seen again and said that he had never been free of the aforementioned symptoms for any length of time during the preceding five years and that of late they had become worse. At this time he also complained of pain on reclining at night. Roentgen examination again showed a duodenal ulcer and hiatal hernia. Four months later another roentgen examination was made, at which time a congenitally short esophagus and a duodenal ulcer were diagnosed. The esophagus ended 6 cm above the diaphragm. Esophagoscopy failed to demonstrate a thoracic stomach.

CASE 5—A 77 year old woman, married, had complained for the past six months of vomiting immediately after meals about every other day. For some time she had noticed also that food when swallowed seemed to stick at the lower part of the chest. For this reason she could eat only soft and semisolid foods. Roentgen examination showed a congenitally shortened esophagus ending 5 cm above the diaphragm with a part of the fundus of the stomach above the diaphragm.

CASE 6—A 51 year old housewife said that for many years she was unable to lie on her left side because of a sensation as of something running up and down inside her chest. Substernal fulness and pain occurred after a meal of coarse foods and about 5 o'clock each morning, relieved by rubbing. Occasional spells of dizziness followed by vomiting were experienced for several years. She always vomited easily, without nausea, and then felt relieved. One of three roentgen examinations showed a congenitally short esophagus. All showed dilatation of the esophagus without obstruction and herniation of the fundus of the stomach through the esophageal hiatus—freely movable.

CASE 7—A 58 year old man gave a history of loss of weight and strength associated with discomfort in the lower part of the abdomen, relieved by reclining, not always associated with ingestion of food or relieved by it. Nausea and vomiting had occurred on four occasions during the past year after eating. Roentgen examination showed a congenitally short esophagus with delay at the third portion. The stomach was above the diaphragm, behind the heart, and fixed upside down. The distal transverse colon and the sigmoid were also herniated through the hiatus. The patient also had pernicious anemia with an initial hemoglobin level of 6.21 Gm and 1,570,000 erythrocytes per cubic millimeter of blood. His anemia was successfully controlled for six years, at the end of which time death followed an attack of pneumonia.

*Symptoms*—Six of the patients with a congenitally short esophagus were troubled with vomiting or regurgitation after ingestion of food. In only a single instance was nausea mentioned. The distress or pain was usually relieved by the regurgitation.

Substernal pain or distress or a feeling of obstruction in this location was present in 5 patients. This occurred either after ingestion of food, especially coarse food, or while the patient was reclining, and frequently was relieved by vomiting.

Abdominal distention, accompanied by gas, occurred in 2 cases, and discomfort in the lower part of the abdomen, relieved by reclining, occurred in 1. Cough, accompanied by asthmatic wheezing, was a prominent complaint of 1 patient, but the evidence is not sufficient to indicate that it was related to the herniation.

Goodall and Hoyt<sup>12</sup> reported dyspnea as the most prominent symptom of 3 patients, 2 of whom probably had complete thoracic stomach. They expressed

<sup>12</sup> Goodall, H. W., and Hoyt, L. H. Thoracic Stomach, Arch Int Med 53:594 (April) 1934.

the belief that the stomach lying within the thorax interfered with respiration, causing dyspnea

It is of interest to note that in our series of patients symptoms which suggest disturbance of the gastrointestinal tract predominated and that they were so distinctive that the diagnosis should have been strongly suspected before roentgen studies were made

Severe anemia was demonstrated in 2 patients. One of them (case 7) had pernicious anemia, the other had rather profuse hemorrhage, which probably resulted from an ulcer at the esophagogastric junction. A third patient had moderately severe anemia. One patient's blood was not examined. In 2 instances a duodenal ulcer was diagnosed, but in neither was there anemia or symptoms strongly suggestive of ulcer.

### HIATAL HERNIA

Mention has already been made of some factors which may influence the development of herniation. Marks<sup>6</sup> and also Levy and Duggan<sup>1d</sup> suggested that obesity is an important contributory factor. Marks expressed the belief that increased intra-abdominal pressure, which may be produced by more than the normal amount of fat in the omentum, a large fibroid or a pregnant uterus, may produce herniation. Rigler,<sup>1c</sup> as mentioned previously, emphasized the importance of pregnancy as a factor. Thirty-seven patients, or slightly more than one half of our series of 72, were women who had been pregnant one or more times.

Trauma is undoubtedly responsible for herniation in some cases. One patient, previously mentioned, had symptoms which were later considered to be the result of a hiatal hernia developing after a fall from a stone wall. Two other patients referred the onset of symptoms to accidents in which their heads were forcibly bumped against the top of an automobile as it went over a bump in the road at a high rate of speed. It seems likely that any one of the factors mentioned might produce herniation in a person with a congenitally defective or relaxed esophageal hiatus whereas none of the same factors might be sufficient to produce herniation in a patient with a normally formed hiatus.

*Symptoms*—The histories of the 7 patients with congenitally short esophagus are included in the following analysis of symptoms because there seemed to be little difference between the two groups. For the same reason the histories of 7 patients who also had pernicious anemia are included.

Pain was the symptom most frequently stressed by the patients. Since the description of the sensations varied greatly from one person to another, it is difficult to know just which expressions of discomfort should be included in this category. The term "pain" is used here to include such recorded sensations as dull or sharp pain, distress, ache, squeezing sensation and feeling of fulness or of obstruction on the swallowing of food.

Fifty-nine of the 72 patients had pain which was believed to be related to hiatal hernia. The pain was said to be in the substernal region by 23 and in the upper part of the epigastrium by 33. 56 patients had some sort of discomfort over an area extending from the middle of the chest to the upper part of the epigastrium. Other sites for the location of pain were the right upper quadrant of the abdomen eight times, right side of the chest three times, the precordial region three times, the left side of the chest, the lower part of the abdomen, the back rarely. If one takes into consideration the facts that the histories were recorded by several physicians and that in many instances hiatal hernia was not suspected, it appears significant that the discomfort was so frequently localized within a rather limited area.

The pain was described as dull (ache or squeeze) by 32 patients and as acute or sharp by 12. It radiated to the abdomen in 9 instances, to the back in 4, to the left arm and shoulder (suggesting anginal pain) in 4, to the right shoulder and arm in 3 and to both the right and the left shoulder in 3.

Discomfort was initiated or aggravated by a meal in 21 instances, by solid food in 9 and by water in 2, making a total of 32 instances in which pain was experienced after ingestion of food or water. Reclining initiated discomfort in 16 cases, whereas exercise, especially that involving the moving or lifting of heavy objects, accounted for the onset in 7. Emotional upsets not infrequently aggravated the condition. Both reclining and lifting are probably much more frequent causes of discomfort than is suggested by these figures. The patient is frequently not aware of the precipitating or aggravating factors, and unless the physician recording the history includes hiatal hernia in his differential diagnosis, these factors may not be brought out in the anamnesis.

Relief from symptoms was attributed to ingestion of an alkaline drink in 7 instances, to that of soft food in 6, to taking of whisky in 1, to vomiting in 14, to use of glyceryl trinitrate in 3, to application of heat in 3, to rest in bed in 2, and to eructation of gas in 1.

Anemia rates second to pain in order of frequency of occurrence as a symptom in our series, and this subject will be discussed later in some detail.

Other symptoms, grouped as they were mentioned in the records, occurred as follows: vomiting, in 32 instances, nausea, in 19, gas in the stomach, in 19, weakness or easy fatigability, in 13, diarrhea, in 10, heartburn, in 9, constipation, in 9, anorexia, in 8, headache, in 7, indigestion, in 4, cough, in 4, nervousness, in 3, insomnia, in 2, dizziness, in 2.

The history most characteristic of patients with hiatal hernia may be summarized somewhat as follows. Following ingestion of food, particularly solid or coarse, there is a feeling of obstruction or pain (ache or squeeze) in the sub-sternal or the upper epigastric region. This may be followed by regurgitation or vomiting, with relief of symptoms.

Discomfort in the same regions as those described in the foregoing paragraph may occur on reclining, especially during the night, and be relieved on arising, or there may be distress after lifting or moving heavy objects. Either reclining or lifting may be followed by hemorrhage, which is in some instances the cause of anemia, as discussed later.

Vomiting and regurgitation of food not associated with nausea are very characteristic complaints. Unexplained indigestion associated with "gas," heart burn or anorexia and easily produced weakness must each lead one to think of hiatal hernia.

Healy<sup>13</sup> summarized the symptoms of his patients as follows: "The most common symptom we found in our cases was substernal pain with regurgitation when in the supine position. The next in order is the vague gastric distress sometimes with tenderness referable to the right upper quadrant and not in the epigastric region, accompanied at times by pain radiating to the back similar to a gall stone attack. Then came vomiting in the morning with hyperacidity. Only in a very few cases did we note difficulty in swallowing solid food at times."

Pancoast and Boles<sup>14</sup> stated that symptoms may be entirely absent but that "probably the most constant, certainly the most suggestive, symptom present is

13 Healy, T. B. Symptoms Observed in Fifty-Three Cases of Non-Traumatic Diaphragmatic Hernia, *Am J Roentgenol* **13** 266 (March) 1925.

14 Pancoast, H. K., and Boles, R. S. Non-Traumatic Left Diaphragmatic Hernia, *Arch Int Med* **38** 633 (Nov) 1926.

pain, often of a colicky nature, localized just above the ensiform or in the epigastrium, which comes on gradually and more often when the patient is lying down, especially at night"

Ohnell<sup>15</sup> found pain in the epigastrium or the immediate neighborhood in 16 and burning or pressure in the same location in 3 of 24 cases reported in the literature. Pain usually occurred immediately or within two to three hours after ingestion of food. Vomiting occurred in 10, regurgitation or heartburn in 6, dysphagia in 4, constipation in 5 and cardiac or pulmonary symptoms in 4 instances.

Goodall and Hoyt<sup>12</sup> have presented in considerable detail the symptom complex observed in their 5 cases, stressing particularly the preponderance of symptoms referable to interference with cardiorespiratory function in 3 patients with thoracic stomach.

Harrington<sup>3</sup> stated that "the chief symptoms of esophageal hiatus hernia are pain, distress, gaseous eructation, vomiting, dyspnea, hemorrhage, weakness, anemia, and palpitation of the heart." He divided the symptoms into those occurring early and those occurring late in the course of the herniation, the main difference being in the severity and the frequency of occurrence. The epigastric distress may be projected through to the back during or shortly after a heavy meal or even after a cup of coffee, and is often relieved by belching of gas and vomiting; this pain is often attributed to cholecystitis.

Jones<sup>8</sup> compared the symptoms of 91 patients with small and 37 with large hiatal hernias. Substernal pain was experienced by more than one third of those with small but by only 5 of those with large hernias. Otherwise there was little difference in the two groups which could be definitely ascribed to the size of the herniation. It is of interest to note that on the basis of the clinical picture a diagnosis of heart disease was made in 13 and of disease of the biliary tract in 22 cases of his series.

These reports and others less concretely summarized, although not in entire agreement in respect to the most characteristic complaints, confirm our own observation that the symptoms are predominantly gastrointestinal in nature and that in a high percentage of instances they are characteristic of the condition so that the diagnosis should be suspected and roentgen examination should merely confirm the diagnosis.

That hiatal hernia occurs more commonly than it is recognized has been noted particularly by Healy,<sup>13</sup> who emphasized the importance of diagnosing the condition correctly so that operations performed because of a confusion of symptomatology would be avoided. Pancoast and Boles,<sup>11</sup> Weitzen,<sup>16</sup> and others have also commented on the importance of avoiding operation on the gallbladder or for peptic ulcer because of failure to recognize the true cause of the symptoms, that is, hiatal hernia.

Roentgenologic recognition of a hiatal hernia even when the presence of the hernia is suspected from the clinical picture is not always possible. At least 14 of our series of patients had been examined by roentgenogram one or more times before the herniation was demonstrated. Two others showed no evidence of herniation after medical treatment had been carried out for several months following demonstration of the hernia. Levy and Duggan<sup>14</sup> reported 4 of 26 cases in which previous roentgen studies had failed to show herniation.

15 Ohnell, H. Hernia diaphragmatica hiatus oesophagei vom intern klinischen Gesichtspunkt, *Acta radiol.* 6 23, 1926.

16 Weitzen, M. Diaphragmatic Hernia with Severe Anemia, *Am J Roentgenol.* 28 808 (Dec.) 1932.

Failure to realize the importance of herniation as the cause of the most disturbing symptoms present in conjunction with those from other pathologic conditions is a common error. Gastroenterostomy was performed in 1 patient because of the presence of a duodenal ulcer, but a few years later the original complaints returned and a hernia was demonstrated. A cholecystectomy not followed by relief of symptoms was recorded in a few instances. Angina pectoris or coronary infarction was believed to be present in several instances, but in only 1 case did an electrocardiographic tracing show evidence of coronary disease, the patient later died of an infarction. A diagnosis of psychasthenia was recorded in a surprisingly large number of instances, apparently because of complaints, often extending over many years, for which no satisfactory explanation in the form of organic disease was demonstrated, although hiatal hernia was known to be present in a few instances.

Earlier in the paper it was mentioned that anemia as a symptom of hiatal hernia was next to pain (or discomfort of a sort sufficiently intense to be classed as pain) in frequency of occurrence. An analysis of the blood was made in 67 of the 72 cases of this series. A diagnosis of pernicious anemia was made in 7 instances and treatment by the usual methods completely controlled the blood levels. In 2 other cases there was severe macrocytic anemia with a high color index, which may best be diagnosed as idiopathic macrocytic anemia.

Forty-seven, or 70 per cent, of the 67 patients tested had hemoglobin levels of 12 Gm or less and 4,000,000 or less erythrocytes per cubic millimeter. If one excludes the 7 patients with pernicious anemia, there were 40, or 66 per cent, with anemia of some degree. Twenty-three patients, or 34.3 per cent, had hemoglobin levels lower than 10 Gm and erythrocyte counts less than 3,300,000. If the 7 patients with pernicious anemia are excluded, there were 16, or 26.6 per cent, with a severe anemia at some time during their observation, possibly caused by the hiatal hernia. In several cases the determination of the blood levels was not done soon enough after a known hemorrhage to demonstrate the maximal degree of anemia.

The cause for the presence of anemia was in some instances open to question, since a gross, severe hemorrhage was not demonstrated in all instances of severe anemia. In a few cases a peptic ulcer or a carcinoma may have been the cause of the hemorrhage observed. Eighteen patients were known to have gross and rather profuse loss of blood. Two others became suddenly dizzy and fell because of weakness, but since neither one consulted a physician for several days, hemorrhage was not demonstrated. A guaiac test of the feces was made in 51 cases, in 18 the result was negative, in 12 it was 1 plus, and in 21 it was 2 plus or stronger.

Peptic ulcer was diagnosed roentgenologically at some time in 9 patients. One with an esophageal ulcer had moderately severe hemorrhage and severe anemia. Two with gastric ulcers had no demonstrable massive hemorrhage, but both had a positive guaiac test of the feces and slight anemia. One of 6 patients with duodenal ulcers had several massive hemorrhages and became severely anemic after each. The diagnosis of duodenal ulcer was made, but the hernia was not demonstrated before he was seen by one of us (W. P. M.). Roentgen studies at the Peter Bent Brigham Hospital demonstrated the herniation, but no ulcer could be visualized. Two of his attacks of hemorrhage occurred in the early morning, after a night in bed, during periods when he was unusually tired, and a third followed the lifting of some heavy boxes and furniture. The patient was advised to have his hernia surgically repaired in order to prevent further hemorrhages. Instead gastroenterostomy was performed in another hospital after a fourth hemorrhage, after which he died from embolism. A positive guaiac test of the feces

was recorded for 3 others of the 6 patients with duodenal ulcers, none of whom was anemic

One of the 2 patients with carcinoma of the stomach had severe hemorrhage and was severely anemic. The other one was not anemic.

It is obvious that the demonstrated peptic lesions could not be responsible for the anemia in a high percentage of instances and that both massive hemorrhage and anemia in this series of patients can probably most commonly be explained on the basis of the hiatal hernia. It is likewise evident that the anemia observed was the result of massive hemorrhage only in a small percentage of instances. It seems likely that the anemia is often the result of prolonged loss of small amounts of blood from the congested esophageal or gastric mucous membrane constricted within the esophageal hiatus. Definite evidence of nutritional deficiency because of an inadequate intake or utilization of food was lacking.

It is difficult to determine the frequency of occurrence of anemia in hiatal hernia in the published series because this aspect has been considered in but few. Harrington<sup>3</sup> reported anemia in 11 per cent of 198 patients on whom he had operated for hernia. The degree of anemia, however, was not mentioned. He emphasized the importance of "secondary" anemia as a clinical manifestation of hiatal hernia. Cowan<sup>17</sup> reported the presence of "secondary" anemia in 13 of 45 cases reviewed but recorded the blood levels in only 2. Marks<sup>5</sup> found erythrocyte levels below 4,000,000 in 7 of 29 patients but stated that not much attention was paid to the anemia. Two of his patients had massive hemorrhage at some time. Levy and Duggan<sup>14</sup> reported anemia in only 1 of 26 patients observed. Weitzen<sup>16</sup> reported 2 patients with the association of anemia and hiatal hernia. Segal<sup>18</sup> reported 2 patients of his own and 3 from the literature in whom the only symptom resulting from hiatal hernia was anemia. He recorded 5 other cases from the literature in which anemia was present. Gardner<sup>19</sup> reported 6 of his own patients and 22 found in the literature in whom severe anemia and hiatal hernia were associated. No other possible cause for the anemia was demonstrated in 20 of these, although the figures recorded indicate that a high color index was present in 1. Blood levels are recorded for only 2 of 10 patients reported by Andrews<sup>20</sup>. One of these was severely, the other moderately, anemic. Neither ulcers nor hemorrhages were observed in her series. Others have also reported isolated instances of anemia. Since these are not related to any series of cases, the incidence cannot be determined.

There is some difference of opinion as to the cause of the anemia observed in patients with hiatal hernia. Harrington<sup>6</sup> spoke of hemorrhage as a not uncommon occurrence. He expressed the belief that it is the result of an ulceration, usually at the lower end of the esophagus, produced by trauma of the incarcerated stomach. He also expressed the belief that these ulcerations are rarely demonstrated by roentgen examination but more commonly by esophagoscopy. Bock, Dulin and Brooke,<sup>21</sup> who reported the presence of "secondary" anemia in 10 patients with hiatal hernia made the comment "Bleeding may be from coexisting ulcer but is usually from mucous congestion."

17 Cowan, I. I. Diaphragmatic Hiatus Hernia, *Am J Roentgenol* **37** 333 (March) 1937

18 Segal, H. L. Secondary Anemia Associated with Diaphragmatic Hernia, *New York State J Med* **31** 692 (June 1) 1931

19 Gardner, K. D. Diaphragmatic Hernia Associated with Secondary Anemia, *Am J M Sc* **185** 561 (April) 1933

20 Andrews, K. S. Diaphragmatic Hernia, with Report of Ten Cases of Oesophageal Orifice Hernia, *Am J Digest Dis & Nutrition* **2** 310 (July) 1935

21 Bock, A. V., Dulin, J. W., and Brooke, P. A. Diaphragmatic Hernia and Secondary Anemia. Ten Cases, *New England J Med* **209** 615 (Sept 28) 1933



The fact that anemia has not been previously associated commonly with hiatal hernia may lead to the impression that our series may be somewhat unusual in that many of the patients might have come to our attention primarily because of an unusual interest in anemia. However, only 15 of the 72 patients are included from the private records of one of us (W P M). The incidence of anemia in this series of patients should lead to a more serious consideration of it as a symptom of hiatal hernia. Hypochromic anemia for which no cause is readily demonstrated, particularly if associated with the symptom complex described, should lead one to suspect seriously the presence of a hiatal hernia.

Gastric analysis was performed in only 34 cases, in 12 of which achlorhydria was shown whereas in 22 essentially normal amounts of acid were found. Seven of the 12 patients with achlorhydria had pernicious anemia. One patient showed achlorhydria at a time when the herniation was demonstrable by roentgenogram, but after a few months of therapy the hernia was not demonstrable, and free hydrochloric acid was found to be present. It seems likely that at the time of the first test the tube did not actually reach the secreting portion of the stomach. This possibility must be kept in mind if the gastric test shows achlorhydria.

Disease of the gallbladder was diagnosed by roentgen examination in 13 patients of the series, and a diagnosis of carcinoma of the gallbladder was made in 1 of these. Diverticulosis of some portion of the digestive tract was demonstrated in 16. There is no reason to believe that any of these conditions was the cause of the anemia.

*Treatment*—Surgical intervention may be necessary in some instances and is desirable particularly if the symptoms indicate that the hernia is becoming more severe. It is a treatment of necessity when there is incarceration of the stomach in the esophageal hiatus with symptoms of obstruction and with recurrence of severe hemorrhage. Ohnell<sup>15</sup> found that 10 of 24 patients whose cases were reviewed as recorded in the literature died from strangulation of the hernia and that 2 died from inanition. He advised medical treatment only for those whose condition was unsuited to surgical treatment. Key<sup>22</sup> and also Pancoast and Boles<sup>14</sup> expressed the opinion that surgical operation is the only effective treatment except in the case of congenitally short esophagus. Harrington<sup>3</sup> likewise supported the concept that surgical operation is the treatment of choice whenever it may be expected to be successful. He has reported 198 cases in which he operated.

The reports found in the literature present little information concerning either the death rate following operations or the extent of successful results in controlling symptoms from which one may draw conclusions in regard to the comparative value of surgical and medical management. Jones<sup>8</sup> expressed the belief that treatment should be essentially medical and that phrenicectomy or surgical repair is justified only for the large hernia or when medical measures fail.

As a result of the evidence presented in our series of cases and particularly as a result of actual use of medical management for those under the private care of one of us (W P M) it may be concluded that the great majority of patients, particularly during the earlier stages of herniation, may be controlled satisfactorily by medical treatment provided the complete cooperation of the patient is obtained. The more severe manifestations, therefore, should be avoided.

Medical management should include the following:

At first the patient should be given a diet low in roughage, with avoidance of solid foods, later the diet should be increased to include some moderately rough and

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<sup>22</sup> Key, E. *Hernia diaphragmatica hiatus oesophagei vom chirurgisch-therapeutischen Gesichtspunkt*, Acta radiol. 6 35, 1926.



coarse foods. Such a diet may include puréed vegetables. It should be divided into five or six small meals daily rather than the customary three larger ones. At no time should the stomach be overloaded. Loss of weight will be desirable in the obese patient.

Patients should be advised to rest before meals. Although some may be able to recline, many will feel better resting in a sitting position or partially reclining. In no case should the patient recline soon after a meal. Those patients whose symptoms occur at night or on reclining will be benefited by sleeping in a semi-reclining position. This may be accomplished by banking pillows, raising the head portion of the mattress, or raising the head of the bed on blocks 3 or 4 inches (7.5 or 10 cm) high.

The patient should be cautioned against lifting heavy objects or lifting any object from a bending over position. All straining and other pronounced physical effort should be avoided, particularly if the patient is obese.

The hypochromic anemia resulting from loss of blood should be treated in the usual manner with optimal doses of iron.

#### CONCLUSIONS

Hernia at the esophageal hiatus is sufficiently clearcut and distinct symptomatically from the commonly recognized pathologic conditions of the upper part of the abdomen and of the thorax that it should be more frequently included in the differential diagnosis of disease in these regions.

Anemia is so commonly associated with hiatal hernia that its presence may be logically explained on the basis of the hernia, and it must be considered an important aid in the diagnosis. It is usually hypochromic and the result of hemorrhage arising from ulceration of the esophageal or of the gastric mucosa or from congestion of the mucous surfaces, produced in either case by mechanical interference by the esophageal hiatus.

The important role of hiatal hernia in the production of certain distressing or incapacitating symptoms and of anemia should be recognized, so that proper medical treatment may be instituted for their relief, which may also prevent the occurrence of the more serious manifestations of the condition.

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# ASSOCIATION OF CIRRHOSIS, THROMBOPENIA AND HEMORRHAGIC TENDENCY

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The hemorrhagic phenomena, so often a complication of hepatic disease, has long presented a serious medical problem, particularly when the disease is severe and of long duration. The isolation of vitamin K and its application to control of the hemorrhagic tendency in hepatic disease created the impetus for study which has increased appreciation of the role of the liver in the synthesis of factors necessary for normal coagulation of blood. For many years thrombin has been known to play a definite part in coagulation of blood, and its precursor, prothrombin, has been shown to be a product of hepatic metabolism. It now is known that a normally functioning liver is one factor necessary for the maintenance of a normal level of prothrombin in the plasma.<sup>1</sup>

Experimentally and clinically, it has been demonstrated that in certain diseases of the liver, a diminished level of prothrombin in the blood often is restored to normal if an adequate amount of vitamin K is made available. However, in severe parenchymal damage to the liver, it is not uncommon to find that despite availability of adequate vitamin K, an adequate concentration of prothrombin cannot be maintained in the blood plasma. This lack of response to the administration of vitamin K can be used as a clinical measure of the degree of hepatic damage present. The quantitative response of prothrombin formation to the administration of vitamin K parallels the clinical state of the liver, and it has been suggested that this response be used as a test to aid in differentiating jaundice due to primary intrahepatic disease from that secondary to obstruction of the biliary passages.

Because of the known effect of the administration of vitamin K on the maintenance of a normal level of prothrombin in the blood in hepatic disease, the administration of this vitamin often is thought to be all that is necessary in cases of such disease to insure a normal clotting time of the blood, and it is forgotten that other factors essential to the complicated physiologic process of blood clotting may be deficient or absent and by their lack prevent normal clot formation. This truth recently was brought rather forcibly to our attention in case 1.

CASE 1—A woman 46 years of age for approximately twenty years had experienced recurrent attacks of epigastric pain without jaundice. Three years prior to her arrival at the Mayo Clinic she had undergone cholecystectomy for calculous cholecystitis, the common duct was not explored. Jaundice followed this operation, and, to correct this, one month later, in May 1938, the common duct was explored and a T tube was inserted. The jaundice cleared and did not return as long as drainage was adequate through the T tube. In April 1939 an unsuccessful attempt was made to anastomose a hepatic duct to the gastrointestinal tract. Jaundice recurred

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From the Division of Medicine, the Mayo Clinic

Read at the First Annual Meeting of the American Federation for Clinical Research, Minneapolis, April 20, 1942

1 Andrus, W D, and Lord, J W, Jr. Clinical Investigations of Some Factors Causing Prothrombin Deficiency. Significance of the Liver in Their Production and Correction, Arch Surg 41 596-606 (Sept) 1940

and never entirely cleared after this procedure. A final unsuccessful attempt to establish a connection between the biliary system and the gastrointestinal tract was made in April 1940.

The patient registered at the clinic in October 1941 because of persistent jaundice, attacks of chills, fever, pruritus and colicky pain in the right upper quadrant of the abdomen, which would extend into the right subscapular region if severe. She did not give a history of a tendency to bleed.

On examination the patient was seen to be markedly jaundiced, the skin had the characteristic bronzing of long-standing icterus. The right side of the diaphragm was elevated to the level of the sixth rib posteriorly and was immobile. The liver and spleen were enlarged and firm, their borders extended approximately 6 cm below the costal edge. The blood pressure was normal. The flocculation test for syphilis gave negative results, albuminuria, grade 2, was present. Roentgenograms of the stomach and colon revealed nothing abnormal. That the liver was damaged considerably was evidenced by a total excretion of hippuric acid of 14 Gm, as compared with a normal excretion of approximately 3 Gm. Macrocytic hypochromic anemia with 9.75 Gm of hemoglobin per hundred cubic centimeters of whole blood was present. The serum bilirubin amounted to 15.2 mg per hundred cubic centimeters. The qualitative van den Bergh reaction was direct. Several preoperative estimations of the prothrombin time by the Quick method gave results varying between seventeen and twenty-three seconds, as compared with a normal value of nineteen seconds.

It was felt that further surgical exploration of the biliary system was advisable, and to this end the patient was prepared in the usual manner by means of a diet high in carbohydrate, low in fat and moderate in protein content. Ten per cent solution of dextrose to which was added thiamine chloride, nicotinic acid amide and ascorbic acid was administered intravenously. A daily dose of 32 mg of 2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate was administered intravenously for two weeks as a source of vitamin K. The Quick prothrombin time was normal on the day of operation. Incision was made through the old abdominal scar, which was found to be thick and dense. At the outset bleeding was encountered so profuse that all the usual measures to control it were unsuccessful. It therefore was necessary to discontinue the operation. The surgeon remarked that the bleeding was so continuously severe that it demonstrated a lack of all tendency to clot. The hemorrhage was controlled finally by pressure, the wound was closed and a transfusion of 500 cc of whole blood was given. The patient made a satisfactory convalescence, and no further tendency to bleed was evident during the remainder of her stay in the hospital.

Our interest was roused by the unusual complication, and further studies were made of the bleeding and coagulating factors of the blood during convalescence. Two platelet counts by the citrate method were, respectively, 68,000 and 56,000 per cubic millimeter of blood. The bleeding time was recorded as six minutes and three and a half minutes on two estimations, the coagulation time was eight minutes, the clot retraction was partial in twenty minutes and complete in fifty minutes. These values are essentially normal with the exception of the obvious reduction in the number of thrombocytes present.

Here, then, was a case in which there was no suggestion before operation of an unusual tendency to bleed. Moreover, the Quick prothrombin time was normal, and thus we have learned to recognize as a safe index of the clotting power of the blood of jaundiced patients. If before operation we had been unduly apprehensive about the hemorrhagic tendency and performed more detailed studies of coagulation time, bleeding time and the number of thrombocytes, our suspicions probably would not have been aroused, because these values, of which all but the last were normal during the convalescent period, probably would have been the same immediately before operation. Fortunately, such a serious hemorrhagic tendency is not often encountered in cases of jaundice when the prothrombin time is normal and an adequate supply of vitamin K has been administered. Since the thrombocytes were the only constituent of blood known to be grossly abnormal, it appeared to us that depletion of them was a significant factor in the hemorrhagic tendency in this case. This observation seemed to deserve further consideration in order that the frequency with which significant thrombopenia is present in cases of severe disease of the liver and its relation to the tendency to bleed in these cases might be determined.

Snell, Vanzant and Judd<sup>2</sup> in 1930 called attention to the occurrence of severe thrombopenia in a case of long-standing hepatic disease and noted that the depression of the thrombocytes in the blood was parallel to the hemorrhagic tendency. We are reviewing briefly this case, which elsewhere is recorded in detail,<sup>2</sup> because it represents one of the first observations of a significant reduction in the blood platelets in a case of severe hepatic damage.

CASE 2—A woman 29 years of age had had cholecystectomy for calculous cholecystitis one year prior to her admission to the Mayo Clinic. Bile began to drain from the wound on the third postoperative day, and jaundice appeared after permanent closure of the biliary fistula ten months later. Deepening of the jaundice was accompanied by mild purpuric manifestations and a tendency to increased menstrual bleeding.

On examination, in addition to the jaundice and purpuric manifestations, mild secondary anemia was noted. After preparation choledochostomy was performed for benign stricture of the common duct, and a T tube was left in place. After operation the tendency to hemorrhage was great and was controlled only by repeated transfusions of blood. The patient made a good recovery and was allowed to return home. When she was seen three months later, her serum bilirubin was found to be 27 mg per hundred cubic centimeters, and the coagulation time was slightly elevated (twelve and one-half minutes). The fistula had continued to drain copious amounts of bile, and her general health was much improved.

The fistula closed spontaneously five months after the operation, and the patient immediately returned to the clinic. At this examination the jaundice had already definitely increased, the serum bilirubin was 47 mg per hundred cubic centimeters. A few days after admission bleeding began from the gums, nose, skin and uterus, and signs of meningeal irritation appeared, which were interpreted as being due to meningeal hemorrhage. The patient became semicomatose and manifested irritability, photophobia and diplopia, and Kernig's sign was present. Repeated transfusions of blood caused temporary improvement. Drainage of bile was reestablished, but there was no improvement in the coagulation factors of the blood. The number of blood platelets per cubic millimeter of blood, which had been 198,000 when the patient was first examined, now ranged between 40,000 and 94,000. The bleeding time determined by the usual technique was normal, but wounds in the skin frequently reopened and bled many days after the puncture was made. The prothrombin time greatly increased. The tourniquet test gave slightly positive results, and the coagulation time varied from twenty to forty minutes. The clot, once it was formed, was normal. Five weeks after the first signs of meningeal irritation the patient suddenly became somnolent. Puncture wounds a week old dribbled blood in a steady stream, and the entire body was covered with great regions of ecchymosis. The venous blood became virtually incoagulable, and death finally resulted.

At necropsy, in addition to the jaundice and external evidence of bleeding noted during life, extensive hemorrhages were found throughout the gastrointestinal tract, the peritoneal cavity, the substance of the lungs and the mucous membrane of the urinary bladder, and there was evidence of severe hemorrhages, both old and new, in the dura mater, the arachnoid and the substance of the brain. The histologic picture of the liver was that of biliary cirrhosis.

The authors in their comment drew particular attention to the depression of the thrombocytes in this case, although they did not claim that this factor was the most significant one in the hemorrhagic tendency. In the light of present knowledge of the value of vitamin K in such cases it is apparent that the administration of this vitamin probably could have changed the clinical course. The prothrombin time was markedly increased, and it is probable that inadequate synthesis of prothrombin by the liver was responsible for the depletion of the prothrombin level in the blood. This inadequate synthesis of prothrombin can be attributed in part to the severe hepatic damage and in part to the inability to utilize what vitamin K was present, because of the complete exclusion of bile from the intestinal tract for such an extended period. It is significant, however, that a profound depletion in blood platelets also was present, and this additional factor undoubtedly contributed in part to the severe hemorrhagic tendency.

These 2 cases represent a distinct type of serious hepatic disease, and in both of them significant thrombopenia was associated. In case 1 the lesion was essentially

2 Snell, A. M., Vanzant, F. R., and Judd, E. S. The Complications and Sequelae of Prolonged Obstructive Jaundice, *M. Clin. North America* 13 1417-1438 (May) 1930.

biliary cirrhosis secondary to severe obstructive jaundice of long standing, in case 2, there was in addition to severe biliary cirrhosis the factor of prolonged extensive loss of bile from the external fistula. That an equally significant depletion in the thrombocytes in the blood with a tendency to bleed is associated with severe hepatic damage of a different type is demonstrated in case 3.

CASE 3—A farmer aged 53, with a good family and personal history, experienced recurrent epigastric distress for fifteen years. He was a moderate user of alcohol and tobacco. Five months before he came to the clinic he noted an exacerbation of his epigastric distress and progressive abdominal enlargement. Coincident with the enlargement of his abdomen purpuric manifestations became evident in the lower extremities, and these were more marked when he spent a great deal of time on his feet. On examination, he was obese, the abdomen was protuberant and dull to percussion and a fluid wave was demonstrable. The liver and spleen were palpably enlarged. Scattered petechiae were observed on the lower extremities, there was cervical and axillary lymphadenopathy. The blood pressure was 100 mm of mercury systolic and 64 mm diastolic. The Kline flocculation test of the blood serum gave negative results. The urine was normal. The concentration of hemoglobin was 13.5 Gm per hundred cubic centimeters of whole blood. The number of leukocytes and the differential count were within normal limits, there was macrocytosis. The concentration of serum bilirubin was 1.4 mg per hundred cubic centimeters, with an indirect van den Bergh reaction. The bromsulphalein test of hepatic function showed retention of dye, grade 1. The bleeding time was one and a half minutes, and the Lee-White coagulation time was nine and a half minutes. The Quick prothrombin time was twenty-two seconds, as compared with a normal of twenty seconds. The number of blood platelets per cubic millimeter of blood estimated on four successive days was respectively, as follows: 78,000, 124,000, 100,000 and 87,000. The values for blood urea, plasma cholesterol and cholesterol esters were, respectively, 28, 225 and 155 mg per hundred cubic centimeters. The serum protein was 7 Gm per hundred cubic centimeters, with an albumin-globulin ratio of 1:1.4. Peritoneoscopy and abdominal paracentesis were performed as a combined procedure. A considerable quantity of straw-colored ascitic fluid was removed, and the liver was seen to be involved by an extensive hobnailed cirrhosis grade 4. The patient was treated by the usual medical measures for cirrhosis, but he failed progressively and died six months later.

#### CIRRHOSIS OF THE LIVER

These observations induced us to review the records in a series of cases of cirrhosis of various types to see how often we would find a significant reduction in the blood thrombocytes in association with severe chronic hepatic disease. The majority of the cases studied were cases of portal cirrhosis, although some were included in which severe damage to the liver, so-called biliary cirrhosis, was secondary to an obstruction of the common duct of long standing. In the last-mentioned cases various degrees of clinical jaundice were associated with various elevations of the serum bilirubin. In each case of portal cirrhosis, injury of the liver was indicated by significant retention of the bromsulphalein dye at the end of one hour, and subclinical jaundice usually was associated with only slight elevation above normal of the serum bilirubin.

For this study we reviewed 80 cases of cirrhosis in which the blood platelet count had been recorded. The counts were made by the citrate method. With this method we have considered the normal concentration of platelets in the blood as from 150,000 to 300,000 per cubic millimeter. Counts varying from 100,000 to 150,000 were designated as borderline and those less than 100,000 as constituting a state of thrombopenia. Since it is known that serious bleeding may occur either spontaneously or as a result of minor trauma when the platelet count falls to less than 50,000, the counts varying from 50,000 to 100,000 were designated as subnormal and those less than 50,000 as critical. In 33 (41.3 per cent) of these 80 cases (table 1) bleeding of any kind did not occur. In 2 (6.1 per cent) of these 33 cases there was definite thrombopenia. In 28 cases (84.8 per cent) of those in which there was no bleeding tendency the platelet count was considered normal. The platelet count did not fall below the critical level in any case in this group. In

47 (58.7 per cent) of the 80 cases of cirrhosis a tendency to bleed was found (table 1). In 12 of these cases (25.5 per cent) a definite thrombopenia was present. In 2 cases the count was below the critical level, being 39,000 and 40,500 respectively. In only 20 cases of this group (42.6 per cent) was the platelet value normal. Bleeding was most commonly from the gastrointestinal tract but also was recorded as coming from the gums, nose, lungs and urinary bladder and occurred into the conjunctival sac and into the skin as purpuric spots and ecchymosis.

It is immediately apparent that the percentage incidence of a normal platelet value in cases of cirrhosis without bleeding was twice that in cases in which some degree of bleeding occurred. In 20 (41.6 per cent) of 48 cases in which the platelet count was normal, some bleeding tendency was present. In a total of 18

TABLE 1—Platelet Count in Cases of Cirrhosis of the Liver With and Without Bleeding

Blood Platelet Count, per Cu. Mm.	Total Cases		With Bleeding		Without Bleeding	
	Number	Per Cent	Cases	Per Cent	Cases	Per Cent
Less than 50,000	2	2.5	2	4.3		
50,000 to 100,000	12	15.0	10	21.2	2	6.1
100,000 to 150,000	18	22.5	15	31.9	3	9.1
150,000 and over	48	60.0	20	42.6	28	84.8
Total	80	100.0	47	100.0	33	100.0
Mean count	197,000		165,000		242,000	

TABLE 2—Cirrhosis. Relation of Platelet Count to Bleeding Time and Lee-White Coagulation Time

Blood Platelet Count, per Cu. Mm.	Bleeding Time			Lee White Coagulation Time		
	Cases	Time Elevated *		Cases	Time Elevated †	
		Cases	Per Cent		Cases	Per Cent
Less than 100,000	9	3	33.3	5	1	20.0
100,000 to 150,000	9	3	33.3	9	1	11.1
150,000 or more	30	8	26.7	26	5	19.2
Total	48	14	29.2	40	7	17.5
Hemorrhagic manifestations	28	9	32.1	23	4	17.4
No hemorrhagic manifestations	20	5	25.0	17	3	17.6

\* Any value of more than three minutes was considered elevated.

† Any value of more than ten minutes was considered elevated.

cases the count was borderline, and in 15 (83.3 per cent) of these bleeding tended to occur. In 10 (83.3 per cent) of the 12 cases in which the count was subnormal there was a tendency to bleeding. In both cases in which a critical count was found bleeding occurred. It is evident that of the cases of cirrhosis studied the tendency for some hemorrhagic manifestation to occur was twice as great in those in which the platelet count was subnormal or borderline as in those cases in which it was in the normal range.

The prothrombin time was estimated in 6 cases, in 3 of these bleeding had not occurred and in 3 bleeding of some type was noted. The prothrombin time was elevated in all but 2 cases, 1 from each group. Since the estimation had been made so infrequently, the incidence cannot be considered significant. In 48 cases the bleeding time was estimated (table 2). It was increased in about 32.1 per cent of the cases in which a hemorrhagic tendency was manifested and in only a slightly less percentage of cases (25 per cent) in which hemorrhage did not occur. This

estimation was too infrequently made to permit any conclusion to be drawn as to the significance of the apparently greater incidence of an elevated bleeding time in the cases of thrombopenia as compared with the cases in which the platelet count was more than 100,000 per cubic millimeter in the group in which hemorrhagic manifestations occurred. The Lee-White test of the coagulation time was of little help in an evaluation of the tendency to bleed in cases of cirrhosis, as is evident by the analysis of 40 cases in which it was performed (table 2)

### SPLENIC ANEMIA <sup>3</sup>

We also reviewed a group of cases of splenic anemia, because of the constant association of hepatic cirrhosis in them. We analyzed the records in a series of 50

TABLE 3—Platelet Count in Cases of Splenic Anemia With and Without Bleeding

Blood Platelet Count, per Cu Mm	Total Cases		With Bleeding		Without Bleeding	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Less than 50,000	1	2.0	1	2.6		
50,000 to 100,000	22	44.0	18	46.2	4	36.4
100,000 to 150,000	14	28.0	11	28.2	3	27.2
150,000 or more	13	26.0	9	23.0	4	36.4
Total	50	100.0	39	100.0	11	100.0
Mean count	126,000		119,000		150,000	

TABLE 4—Splenic Anemia. Relation of Platelet Count to Bleeding Time and Lee-White Coagulation Time

Blood Platelet Count, per Cu Mm	Bleeding Time			Lee White Coagulation Time		
	Cases	Time Elevated *		Cases	Time Elevated †	
		Cases	Per Cent		Cases	Per Cent
Less than 100,000	13	3	23.0	4	1	25.0
100,000 to 150,000	9	9	100.0	4	0	0.0
150,000 or more	6	0		1	0	
Total	28	12	42.9	9	1	11.1
Hemorrhagic manifestations	23	10	43.5	7	1	14.3
No hemorrhagic manifestations	5	2	40.0	2	0	

\* Any value of more than three minutes was considered elevated

† Any value of more than ten minutes was considered elevated

cases in which platelet count was recorded prior to splenectomy (table 3). In 11 (22 per cent) bleeding had not occurred. In 4 of these 11 (36.4 per cent) there was definite thrombopenia, in 4 the platelet count was normal. In 39 cases a tendency to bleed was present. In 19 of these cases (48.8 per cent) definite thrombopenia was present, and in 1 the count was below the critical level. In 9 cases (23 per cent) in which some form of bleeding had occurred the platelet count was normal. In the cases of splenic anemia the bleeding was most frequently from the gastrointestinal tract, although it also occurred from the gums, nose and vagina and into the skin and the sclera of the eye. It is noteworthy that the percentage incidence of thrombopenia is definitely higher in the cases in which there was a hemorrhagic tendency than in those in which bleeding did not occur,

3 In this communication the term splenic anemia is applied to that group of conditions sometimes termed Banti's disease, in which there is a marked anemia and splenomegaly and associated leukopenia. In all of our cases hepatic cirrhosis was present.

although the contrast is less striking than it was in the cases of cirrhosis of the liver previously cited. In only 3 cases was a record made of the prothrombin time, and in every instance this was normal. In this group of cases, as in those of cirrhosis, an estimation of the bleeding time was an unreliable index of the bleeding tendency (table 4). This comment applies also to the Lee-White coagulation time (table 4) although it is apparent that these factors were estimated too infrequently to provide the basis for any deduction.

## COMMENT

Thrombopenia occurred in a significant percentage of cases of splenic anemia. This is in accord with the observations of others. It is worthy of comment that in our cases of hepatic cirrhosis definite thrombopenia occurred in 17.5 per cent, although this incidence is less than half that in the cases of splenic anemia, it is significant. The fact that when the incidence of hemorrhagic phenomena is compared in regard to cirrhosis (58.8 per cent) and splenic anemia (78 per cent) it is greatest in the cases in which the incidence of thrombopenia is highest does not seem to us a chance observation.

King<sup>4</sup> in 1929 studied 100 cases of portal cirrhosis and found that in 72 a record of the number of blood platelets had been made. It was subnormal in 20 per cent. This figure compares with an incidence of thrombopenia of 17.5 per cent in our cases of hepatic cirrhosis. In King's series abnormal bleeding and clotting times were noted concurrently with a subnormal platelet count in only 2 cases. Howar<sup>5</sup> found a definite diminution of the platelet count in 50 per cent of a small series of cases of cirrhosis but found no constant relation between the reduction of the platelet count and an alteration in the bleeding time. Abrami<sup>6</sup> noted a tendency toward thrombopenia in hepatic disease. Alt and Swank<sup>7</sup> noted almost complete disappearance of thrombocytes with purpura in a case of catarrhal jaundice. Alt, Carroll and Doherty<sup>8</sup> noted a similar case in which severe hemorrhagic manifestations were present. Fellingner and Klima<sup>9</sup> observed thrombopenia in clinical cirrhosis of the liver. Experimental substantiation of these clinical observations occurs in the report of Higgins and Stasney,<sup>10</sup> who found that when cirrhosis of the liver was produced in rats by the administration of carbon tetrachloride the thrombocytes in the peripheral blood stream diminished and that when severe cirrhosis occurred the number of thrombocytes was reduced to almost a third of normal.

It therefore appears that the thrombopenia which is an accompaniment of severe hepatic disease in a significant percentage of cases is not an unimportant phenomenon. We have seen in the summaries of the cases reported and in the analysis of the group of cases studied that this thrombopenia appears to play some part in the tendency to bleed which often is manifest in these cases. Since the

4 King, R. B. The Blood Picture in Portal Cirrhosis of the Liver. A Report Based on One Hundred Cases, *New England J. Med.* **200** 482-484 (March 7) 1929.

5 Howar, B. F. Hematologic Studies in Liver Disease, *J. Iowa M. Soc.* **28** 148-150 (April) 1938.

6 Abrami, P. Le purpura des hépatiques, *Ann. de med.* **37** 71-79 (Jan.) 1935.

7 Alt, H. L., and Swank, R. L. Thrombopenic Purpura Associated with Catarrhal Jaundice. Report of a Case, *Ann. Int. Med.* **10** 1049-1054, (Jan.) 1937.

8 Alt, H. L., Carroll, H. B., and Doherty, C. C. Thrombopenic Purpura Associated with Catarrhal Jaundice, *Northwestern Univ. Bull., M. School* **14** 183-186, 1940.

9 Fellingner, K., and Klima, R. Lebercirrhose und Anämien, *Ztschr. f. klin. Med.* **126** 547-567, 1934.

10 Higgins, G. M., and Stasney, J. The Peripheral Blood in Experimental Cirrhosis of the Liver, *Folia haemat.* **54** 129-144 (Feb.) 1936.



only known function of the blood platelet is concerned with the mechanism of blood clotting, it is readily apparent that a considerable disturbance from normal of this constituent of blood may have important effects. For example, rupture of an esophageal varix would be an especially serious complication in a case in which the platelet count was less than 50,000, because there would be little if any tendency for a clot to form, even if the platelet count were between 50,000 and 100,000, the formation of a firm clot would be seriously impaired. Best and Taylor<sup>11</sup> suggested that perhaps one of the functions of the platelets in the mechanism of blood clotting is the liberation of the important substance prothrombasc. Eagle<sup>12</sup> stated that the physiologic role of the platelets in coagulation is their enormous acceleration of the production of thrombin. Whether a platelet factor actually combines with prothrombin or merely accelerates a reaction which proceeds slowly even without it is not known. Consideration of the exact biochemical role which the blood platelets play is not within the purpose or scope of this paper. That the blood platelet is important and that a normal concentration is necessary in the maintenance of normal health is apparent when one considers such clinical manifestations of abnormal concentrations as thrombopenic purpura and its hemorrhagic complications. Since it is evident that a significant degree of thrombopenia coexists with severe hepatic disease in some cases, it is immediately apparent that this factor at times may modify seriously and complicate the hemorrhagic tendency, which has so long been a stumbling block in the care of patients who have severe hepatic damage. That the one factor of thrombopenia apparently can be the basis for a severe hemorrhagic tendency is suggested in case 1. It is well known that in serious hepatic damage associated with disturbance in the prothrombin level of the blood, adequate administration of vitamin K sometimes is ineffective in rectifying the lack of prothrombin. It has been suggested that this failure is due to an inability on the part of the severely damaged liver to utilize the vitamin in the synthesis of prothrombin. It is well to remember, however, that even though the administration of this vitamin brings about a normal state of prothrombin in the blood, there may still be the hazard of hemorrhage from other equally important associated factors. Fortunately, this problem does not confront one often in cases in which surgical intervention is needed. However, we feel that this study serves to emphasize that in cases of severe hepatic disease more than one factor may be at fault in bringing about an abnormal state of coagulability of the blood, it emphasizes the need to evaluate these cases from every standpoint and suggests that, although general understanding of the bleeding tendency in hepatic disease has been much improved in recent years, the problem is not solved completely. Undoubtedly other avenues of investigation must be explored before one can hope to reach a complete understanding of this complicated and important matter.

#### SUMMARY AND CONCLUSIONS

It is important to call attention to the possibility that factors other than the concentration of prothrombin may be of significance in explaining the aberrations from normal noted in the mechanism of coagulation of blood in cases of severe damage to the liver. Our attention was recently turned to the possibility that thrombopenia might be an important factor in explaining the severe hemorrhagic tendency sometimes encountered in hepatic disease. A series of 80 cases of hepatic

11 Best, C. H., and Taylor, N. B. *The Physiological Basis of Medical Practice*. A University of Toronto Text in Applied Physiology, Baltimore, William Wood & Company, 1937.

12 Eagle, H. *Studies on Blood Coagulation. I. The Role of Prothrombin and of Platelets in the Formation of Thrombin*, *J. Gen. Physiol.* **18** 531-545 (March 20) 1935.

cirrhosis was reviewed and definite thrombopenia was found in 17.5 per cent. Although a definite hemorrhagic tendency was evident in many of these cases regardless of the level of the blood platelets, it was relatively twice as frequent when thrombopenia was associated. However, a hemorrhagic tendency is not exhibited in all cases of thrombopenia, for in 2 of a total of 14 cases of cirrhosis and thrombopenia bleeding of any kind did not occur.

The records in 50 cases of splenic anemia also were studied. The incidence of thrombopenia was higher than in the cases of cirrhosis, and the incidence of bleeding was increased correspondingly. In these cases, as in those of cirrhosis, the tendency to bleed was greater with a significant reduction in the level of thrombocytes.

We believe that the diminution of the blood platelets in severe hepatic disease of long standing is not a chance and unimportant finding. In our study we did not discover an explanation for this alteration, but we feel that in its presence the bleeding hazard is definitely increased. Our observations serve to emphasize the complexity of the important problem of bleeding in hepatic disease and suggest that further exploration of the various factors concerned will be necessary to clarify it.

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# STUDIES IN SYPHILIS

## I REVIEW OF THE INCIDENCE OF SYPHILIS IN AUTOPSIES ON ADULTS

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Clinical investigations of the biology of syphilitic infection have been directed essentially to the elucidation of the problems of diagnosis, therapy and its complications, end results and serology. By its very nature, the clinical approach has been practically limited to the study of the disease in the viable host, and as a result many tangential issues have received no more than cursory and scattered attention. It is apparent that the coordination and correlation of the clinical aspects of the disease with the observations at autopsy will throw light on many problems which are still in the penumbra of knowledge. How frequently do persons with clinically diagnosed syphilis present morphologic evidence of syphilis at autopsy? What is the relationship between clinical cure and morphologic lesions at death? How often does a person with clinically diagnosed syphilis die as a direct result of his disease, and how often is the disease a contributory or a noncontributory factor in causing death? Is the distribution of the causes of death among persons with syphilis, apart from this disease, any different from that of the nonsyphilitic population? Of corollary interest, does syphilis confer any susceptibility or resistance to other diseases? What for instance, is the probability of death from cancer or from other morbid processes among syphilitic as compared with nonsyphilitic persons? Is there any correlation between serologic observations and morphologic evidence of syphilis at death? How does the longevity of the syphilitic person compare with that of the nonsyphilitic?

A stimulating paper by Moore<sup>1</sup> tersely summarized many unknowns in syphilology and indicates the range of our primary interest.

In spite of 400 years of study, we still do not know the actual importance of syphilis as a cause of death. To what extent does death directly from syphilis masquerade under other diagnoses, or to what extent is syphilis an indirect cause of death from other conditions?

The modern necropsy studies of syphilitic patients, such as those of Warthin, provide no answers to these questions. Such studies, while revealing a very high incidence of lesions of syphilis, especially in aorta, heart, meninges and testes, provide no correlation between the clinical status and the necropsy findings, no information as to cause of death, and no data as to the kind and amount of treatment, if any, given during life. What is clearly here needed is a detailed study of both clinical and necropsy data in a very large series of patients,

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Since this paper was submitted, two reports in the series have been published. Black-Schaffer, B., and Rosahn, P. D. Studies in Syphilis. II. Methods of Analysis of Yale Autopsy Protocols, Including a Code for the Punched Card Study of Syphilis, *Yale J Biol & Med* **15** 575, 1943. Rosahn, P. D., and Black-Schaffer, B. Studies in Syphilis. III. Mortality and Morbidity Findings in the Yale Autopsy Series, *ibid* **15** 587, 1943.

1. Moore, J. E. Unsolved Clinical Problems of Syphilology, *Am J Syph, Gonorr & Ven Dis* **23** 701, 1939.

to provide information as to the frequency with which patients recognized as syphilitic during life, either on clinical or laboratory grounds, showed lesions of syphilis at necropsy and what these lesions, if any, were, the frequency with which patients adequately studied during life with no discoverable evidence of syphilis showed such evidence at necropsy, the relationship of clinically or pathologically recognized syphilis to the final illness and the direct or indirect cause of death, the relationship of necropsy evidence of syphilis to treatment during life, and a dozen similar factors as yet unknown

These and other related problems form the background for a survey now in progress. The basis for this study consists of 5,300 autopsies performed in the department of pathology at the Yale University School of Medicine since 1917. Supplementary and complementary information has been derived from a review of the pertinent literature. The present report constitutes the first paper in the series and is devoted to a critical review of the available literature on the incidence

TABLE 1—*Incidence of Syphilis at Autopsy Among Persons Aged 20 and Over*

Author *	Country	Years	Number of Autopsies	Persons with Syphilis	
				Number	Per Cent
Hervheimer †	Germany	1906-1930	10,400	270	2.60
Beil † <sup>10</sup>	U S A	1910-1937	19,785	601	3.04
Gürich ‡	Germany	1911-1924	23,179	806	3.48
Hansteen §	Norway	1907-1925	11,376	515	4.53
Teodori † <sup>11</sup>	Italy	1918-1935	7,673	371	4.84
Fratesi † <sup>12</sup>	Italy	1928-1933	8,217	418	5.09
Meinhof † <sup>13</sup>	Denmark	1911-1920	4,594	245	5.30
Langer	Germany	1906-1925	23,015	1,268	5.51
Guldberg ‡ <sup>22</sup>	Norway	1896-1930	8,215	491	5.84
Simmers † <sup>11</sup>	U S A	1906, 1916	5,000	314	6.28
Nickel ‡ <sup>20</sup>	Germany	1907-1931	11,476	827	7.21
Ogden ‡ <sup>12</sup>	U S A	1911-1928	5,408	418	7.73
Ophuls ~	U S A	1900-1923	2,192	280	11.24
Koppisch °	Porto Rico	1926-1938	665	75	11.30
Manohar §	India	1927-1934	2,721	431	15.84
Hahn °	U S A	1922	850	179	21.06
Warthin °	U S A	1909-1929	1,675	491	29.49
Total (7 different countries)		1896-1938	146,761	7,993	5.45

\* The symbols (†, ‡, § and ||) refer to footnotes to the table. Superior figures refer to footnotes throughout the text.

† Hervheimer, J. Syphilitische Veränderungen des Herzens und der Arterien, in Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 16, pt. 2.

‡ Gürich, Ueber die syphilitischen Organveränderungen die unter dem Sektionsmaterial der Jahre 1914-1924 angetroffen wurden, München med. Wehnschr. 72: 950, 1925.

§ Hansteen cited by Guldberg.<sup>22</sup>  
|| Langer, D. Die Häufigkeit derluetischen Organveränderungen, insbesondere der Aortitis luetica, München med. Wehnschr. 73: 1782, 1926.

of syphilitic infection in adults as determined by various autopsy studies. Other reports bearing on the general problem will follow.

The literature on the pathologic changes of syphilis contains no comparative or summated analysis of the isolated surveys of autopsy populations that have appeared from time to time. Many authors have directed their attention to specific types of syphilitic lesions, and as a result the scope of their studies has been limited to particular organ systems or to special tissue reactions. Comparatively few investigators have been concerned with the incidence of syphilis at autopsy in its broadest, all-inclusive aspects, and many of their studies have appeared in foreign publications not readily accessible in America.

It is the principal purpose of this paper, therefore, to collate and evaluate the available reports on the frequency of morphologically diagnosed syphilis in autopsy populations. The review to be presented is concerned with syphilis in its acquired form, and for convenience in analysis the autopsy populations have been limited to persons aged 20 and over. Wherever necessary published reports have been recast to give the incidence of syphilis by decades beginning with the

age of 20, this revision, however, in no way altering the factual data presented by the author. It is admitted at the outset that there may be included a certain small number of syphilitic persons over 20 whose infection was congenital, but these are adequately counterbalanced by the exclusion of persons under 20, some of whom no doubt had acquired syphilis. At any rate, the populations under consideration are large enough to reduce effectively any error introduced by taking the age of 20 as the arbitrary lower limit of acquired syphilis.

Table 1 presents a summary of available reports on the incidence of syphilitic lesions in autopsy populations. The data of this table are graphically depicted in chart 1. Four countries of Continental Europe, one in Asia, one West Indian island and the United States are represented. The frequency of syphilitic changes encountered at autopsy among persons over 20 years of age varies from a low

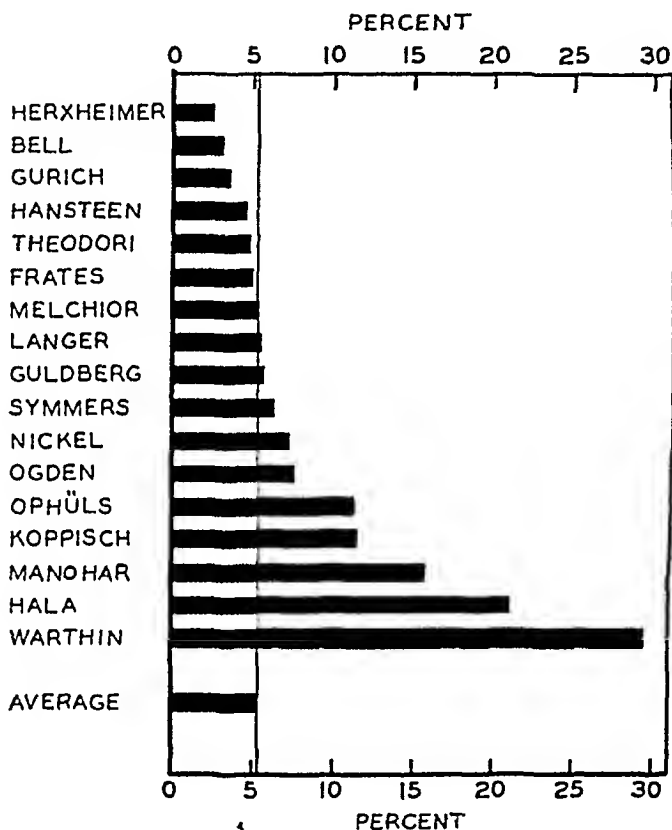


Chart 1—Incidence of syphilis at autopsy among persons over 20 years of age

of 2.6 per cent to a high of 29.5 per cent. The average for all of the seventeen reports presented in the table is 8.8 per cent. This average, however, gives equal weight to each of the reports regardless of the number of observations on which it was based. An alternative average value is one based on the entire summated autopsy population in the seventeen reported series. Of a total of 146,761 persons, 7,993, or 5.45 per cent, were observed to be syphilitic at autopsy.

Other reports on the incidence of syphilitic lesions at autopsy are available, but for the stated reasons they were not incorporated in table 1. Brines<sup>2</sup> studied 618 routine autopsies performed in 1934 at the City of Detroit Receiving Hospital, where 36 per cent of the patients admitted were Negroes. He found 54 instances of gross and microscopic syphilis, an incidence of 8.7 per cent, but failed

<sup>2</sup> Brines, A. O. Laboratory Diagnosis of Syphilis, in Papers of the Michigan Academy of Science, Arts and Letters, Ann Arbor, Mich., University of Michigan Press, 1936, vol. 21, p. 561.

to give the age and sex composition of the autopsy group. Turnbull<sup>3</sup> studied more than 7,000 necropsies performed in London between 1908 and 1913 and found that approximately 4 per cent had disclosed lesions of acquired syphilis. Incomplete data prevent an exact computation of incidence. Pohlen<sup>4</sup> reviewed 8,182 autopsies performed in Magdeburg between 1928 and 1936. Of the subjects studied, 557, or 6.8 per cent, had morphologic evidence of syphilis. This figure includes both those with congenital and those with acquired lesions, who cannot be readily segregated on the basis of the data as given.

Twelve of the seventeen reports listed in table 1 showed an incidence of syphilis of less than 8 per cent, while only five authors gave an incidence higher than 11 per cent. A comparison of individual results shows a striking variation between those of Warthin,<sup>5</sup> Hala,<sup>6</sup> Ophuls,<sup>7</sup> Manohar<sup>8</sup> and Koppisch,<sup>9</sup> on the one hand, and the remaining authors, on the other. If we place the summated observations of these five authors in one classification and compare their results with those of the remaining authors, the difference is striking.

Authors	Autopsies, Number	Instances of Syphilis	
		Number	Per Cent
Warthin, Hala, Ophuls, Manohar and Koppisch	8,403	1,459	17.36
12 others	138,358	6,534	4.72

It is, moreover, apparent that as regards reports emanating from the United States, there are two clearcut and distinct schools of opinion. The first school, represented by Bell,<sup>10</sup> Symmers<sup>11</sup> and Ogden,<sup>12</sup> reported 1,333 instances of syphilis among 30,193 autopsies on persons aged 20 and over, a frequency of 4.4 per cent. Warthin,<sup>5</sup> Hala<sup>6</sup> and Ophuls,<sup>7</sup> representing the second school, found 953 cases of syphilis in an autopsy population of 5,017, an incidence of 19 per cent. The marked disparity between these two sets of results represents one of the outstanding problems of modern syphilology.

It is conceivable that the differences are real and characteristic of the different populations under investigation. On this basis syphilis was actually ten times as frequent in the population studied by Warthin as in that surveyed by Bell. If it is true that treatment effectively eliminates all morphologic traces of syphilis, the variable incidence might be explained by differences in the availability and intensity of syphilotherapy in the several communities forming the reservoirs for the different autopsy populations. Information on this point is outside the range of the present report, but other considerations suggest that the entire explanation

3 Turnbull, H. M. Alterations in Arterial Structure and Their Relation to Syphilis, *Quart J Med* **8** 201, 1914-1915.

4 Pohlen, K. Ueber die Häufigkeit der Syphilis und der syphilitischen Folgezustände nach dem klinischen und pathologischen Befund, *Dermat Wchnschr* **105** 1469, 1937.

5 Warthin, A. S. The New Pathology of Syphilis, *Am J Syph* **2** 425, 1918, The Role of Syphilis in the Etiology of Angina Pectoris, Coronary Arteriosclerosis and Thrombosis, and of Sudden Cardiac Death, *Am Heart J* **6** 163, 1930.

6 Hala, W. W. Incidence of Syphilis, *Am J Syph* **6** 616, 1922.

7 Ophuls, W. A Statistical Survey of Three Thousand Autopsies, Stanford University Pub., Univ Series, M Sc **1** 234, 1926.

8 Manohar, K. D. Incidence of Syphilis, *Indian J Ven Dis* **1** 9, 1935.

9 Koppisch, E. La sífilis en Puerto Rico. Estudio basado en la revisión de 1000 autopsias consecutivas (informe preliminar), *Bol Asoc med de Puerto Rico* **31** 160, 1939.

10 Bell, E. T. Frequency with Which Syphilitic Lesions Are Encountered in Postmortem Examinations, *Arch Path* **26** 839 (Oct) 1938.

11 Symmers, D. Anatomic Lesions in Late Acquired Syphilis, *J A M A* **66** 1457 (May 6) 1916.

12 Ogden, M. A. Aneurysm of the Aorta, *Urol & Cutan Rev* **44** 731 1940.

does not lie in this direction. In the first place, the primary premise, that treatment effectively eradicates the morphologic changes of syphilis, is a problem yet to be settled. In the second place, even if this premise were accepted, the necessary conclusion that syphilis is treated more than four times as effectively in New York, where Symmers found an incidence of 63 per cent, than in Michigan, where Warthin reported a 29.5 per cent frequency, would appear untenable.

Other factors, such as variability in economic status, in race, in age and in sex distribution of the subjects comprising the different autopsy populations, are of importance, and these will be discussed in subsequent paragraphs. A critical analysis of the diagnostic criteria employed by the different authors may also throw some light on their widely divergent findings.

#### RACE

It is well known that syphilis is much more frequent in the American Negro than in the white race. Keidel and Moore,<sup>13</sup> among 5,000 patients admitted to the medical ward of Johns Hopkins Hospital, found positive Wassermann reactions of the blood in 76 per cent of the white persons and in 22.9 per cent of the Negroes. Among 4,000 discharged medical patients, syphilis was diagnosed in 97 per cent of the white persons and in 25.4 per cent of the Negroes. Other authors, notably Turner<sup>14</sup> and Paullin, Davison and Wood,<sup>15</sup> have reported comparable results. However, it is not possible to explain the divergent results summarized in table 1 entirely on the basis of the racial composition of the different autopsy populations. All of the European patients were adult Caucasians, and this is true also of Warthin's group. The population studied by Ophuls was composed of 91.3 per cent white persons, no attempt having been made to correlate race with morphologic changes, because of the small number of Negroes. Hala and Symmers made no mention of the racial composition of their groups. In Koppisch's series the incidence of syphilis among white persons was 86 per cent, as contrasted to an incidence among mulattoes of 13.8 per cent and among Negroes of 16.9 per cent. These last two groups comprised 37.5 per cent of the population and contributed 52 per cent of the syphilitic subjects. It is thus seen that the relatively high incidence of syphilis reported by Koppisch can be accounted for at least in part by the inclusion of a large number of mulattoes and Negroes, in whom the disease is more frequent than in the white race. Ogden's autopsy group consisted of 2,280 white persons, 89 of whom had syphilis, an incidence of 4 per cent, and 3,128 Negroes, 329 of whom had anatomic syphilis, an incidence of 10.5 per cent. Manohar's observations will receive more detailed discussion later. The cardinal point with regard to race is that, although syphilis is demonstrably more frequent in the Negro than in the white person, the racial composition of the different populations is alone insufficient to explain the diverse results. Warthin, reporting the highest incidence, studied a population consisting solely of white persons.

Manohar requires special consideration because he was dealing with natives of India, a racial group not comparable to any investigated by the European and American authors. His series consists of two groups. The first was composed of 882 persons autopsied at the Grant Medical School, in Bombay. Syphilis was

13 Keidel, A., and Moore, J. E. The Wassermann Reaction in the Johns Hopkins Hospital, *Bull. Johns Hopkins Hosp.* **34** 16, 1923.

14 Turner, T. B. The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases, *Bull. Johns Hopkins Hosp.* **46** 159, 1930.

15 Paullin, J. E., Davison, H. M., and Wood, R. H. The Incidence of Syphilitic Infection Among the Negroes in the South, *Boston M. & S. J.* **197** 345, 1927.

diagnosed at autopsy in 207 per cent of these. The second comprised 1,839 persons autopsied by police surgeons, among whom 13.1 per cent had lesions of syphilis. In the latter group only the principle cause of death was investigated, while the first was thoroughly studied by complete gross examinations. This author recorded the remarkable observation that 49 per cent of the persons autopsied at the medical school had syphilitic lesions of the heart, generally recognizable on gross examination. This observation, which is at complete variance with the entire literature, is explicable only on the basis of the author's diagnostic criteria. These, however, he fails to describe.

#### SOCIAL AND ECONOMIC STATUS

It is difficult to evaluate the social and economic status of the autopsy populations studied by the various authors listed in table 1. Most of the reports are

TABLE 2—Frequency of Syphilitic Lesions in Men and in Women as Diagnosed at Autopsy by Five Different Investigators

Author	No of Autopsies	Men, Total		Women, Total		Persons with Syphilis			
		No	Per Cent	No	Per Cent	Men		Women	
						No	Per Cent	No	Per Cent
Bell	19,785	13,103	66.2	6,682	33.8	480	3.6	121	1.8
Frates	8,217	5,217	63.5	3,000	36.5	314	6.0	104	3.4
Koppisch	605	494	74.3	171	27.7	65	11.8	10	5.8
Mehlhor	4,594	2,482	54.0	2,112	46.0	171	6.9	74	3.5
Teodori	7,673	4,222	55.0	3,451	45.0	300	7.1	124	3.5
Total	40,934	25,518	62.3	15,416	37.7	1,830	5.2	433	2.8

TABLE 3—Frequency of Syphilitic Lesions in Men and in Women as Diagnosed in Five Different Investigators (Observed and Expected Values Summated from Table 2)

Sex	Syphilitic		Nonsyphilitic		Total
	Observed	Expected	Observed	Expected	
Men	1,830	1,009	21,188	24,419	25,518
Women	433	664	14,983	14,752	15,416
Total	1,763	1,763	39,171	39,171	40,934

based on persons in the general category "city hospital patients." There were private patients in the series studied by Bell and in the populations analyzed by several of the German and Scandinavian authors. From this viewpoint alone, the 29.5 per cent incidence of syphilis in Warthin's group of "private patients" is noteworthy.

#### SEX

Only five of the authors named in table 1 have published sufficient information to relate sex to acquired syphilis demonstrable by lesions at autopsy. Their reports are summated in tables 2 and 3. Of 40,934 autopsied persons over 20, 62.3 per cent were men and 37.7 per cent women. Among these, 1,763 had evidence of syphilitic infection, of whom 75.4 per cent were men and 24.6 per cent were women. Thus, whereas approximately three fifths of the autopsy population were men, men accounted for three fourths of the cases of syphilis. Analysis by the chi-square test of homogeneity (table 3) indicates a statistically significant difference between these values. It can be concluded that a higher proportion of men and a lower



proportion of women showed evidence of syphilis at autopsy than could be expected on the basis of the proportions of the sexes in the combined populations. Syphilis was diagnosed in 52 per cent of the male population, a significantly higher percentage than that observed among women, i e, 28 per cent.

Each of the five authors presenting data on the sex incidence of syphilis at autopsy reported a frequency among males approximately twice that observed among females. Unfortunately the reports of four authors, namely, Ophuls, Manohar, Hala and Waitlin, who found the highest incidence of syphilis, do not lend themselves to an analysis of the sex distribution either of their total autopsy population or of their syphilitic population. A critical evaluation of their material in the light of this general conclusion with regard to sex is therefore not feasible.

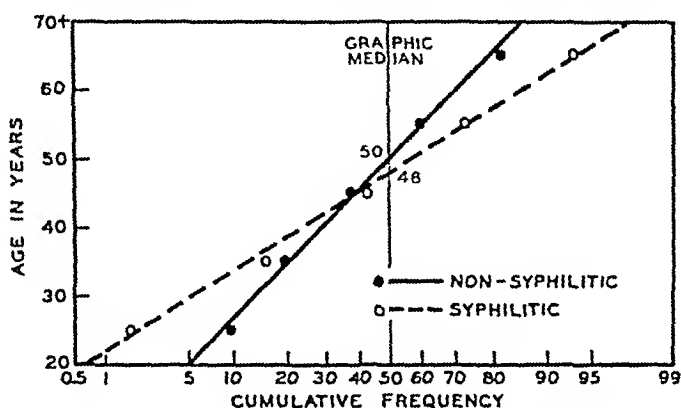


Chart 2—Age of men with and without syphilitic lesions at autopsy

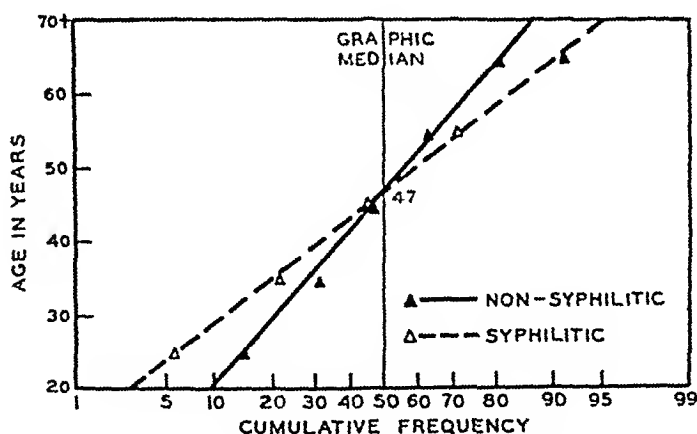


Chart 3—Age of women with and without syphilitic lesions at autopsy

It is, however, justifiable to conclude that the varied incidence of syphilis encountered by the different observers cannot be wholly the result of a preponderance of males in their autopsy populations.

#### AGE

The data presented by Teodori,<sup>16</sup> Bell,<sup>16</sup> Frates,<sup>17</sup> Melchior<sup>18</sup> and Koppisch<sup>9</sup> are the only published reports sufficiently exhaustive to permit of a summated

16 Teodori, U. Rilevi statistici concernenti la sifilide nel materiale autoptico dell'Istituto di Anatomia Patologica di Firenze dal 1918 al 1935 con rilievi comparativi sulla frequenza dei tumori maligni e della tubercolosi, *Dermosifilograf* 13 143, 1938

17 Frates, A. Considerazioni statistiche sulla sifilide nelle prime 10,000 autopsie dell'Istituto di Anatomia Patologica della R Università di Milano, *Clin med ital* 65 1015, 1934

18 Melchior, L. Om sektionsfund og dødsårsager hos patienter med erhvervet syfilis, *Ugeskr f læger* 84 1351, 1922

analysis of the incidence of syphilitic lesions at autopsy in relation to age at death. The findings of these five authors form the basis for the following discussion of age and syphilis in men at autopsy. The last author's data are not included in the consideration of age and syphilis in women because of the small number of women in his series. The summated data are presented in table 4 and charts 2, 3 and 4. The figures were drawn on arithmetical probability paper and show the cumulative percentages by decades. A normal frequency distribution when charted on this type of paper is represented by a straight line. Deviation from a straight line is indicative of corresponding deviation from a normal distribution. The median is easily determined graphically by the intersection of the 50 per cent ordinate with the frequency curve. The slope of the frequency line indicates the degree of variability of the data: the steeper the slope, the greater the variability (Schiek<sup>19</sup>).

The mean age (chart 4) of nonsyphilitic men over 20 was  $54 \pm 0.14$  years, a value significantly higher than that found for nonsyphilitic women,  $52.09 \pm 0.23$

TABLE 4—*Analysis of Sex Distribution of Persons With and Without Syphilitic Lesions at Autopsy*

Age	Nonsyphilitic			Syphilitic		
	Number	Per Cent of Total	Cumulative per Cent	Number	Per Cent of Total	Cumulative per Cent
Men *						
20-29	2,220	9.2	9.2	22	1.7	1.7
30-39	2,356	9.7	18.9	173	13.4	15.1
40-49	4,159	18.4	37.4	358	27.7	42.8
50-59	5,375	22.2	59.6	381	29.5	72.3
60-69	5,384	22.3	81.9	272	21.1	93.3
70+	4,391	18.2	100.0	86	6.7	100.0
Total	21,192	100.0		1,292	100.0	
Women †						
20-29	2,191	14.8	14.8	21	5.3	5.3
30-39	2,297	15.5	30.2	62	15.5	20.8
40-49	2,384	16.1	46.3	95	23.8	44.5
50-59	2,983	16.1	62.3	106	26.5	71.0
60-69	2,716	18.3	80.6	80	20.0	91.0
70+	2,874	19.4	100.0	56	9.0	100.0
Total	14,845	100.0		400	100.0	

\* The data are based on the reports of Bell, Frates, Koppisch, Melchior and Teodorl.

† The data are based on the reports of Bell, Frates, Melchior and Teodorl.

years. The mean age of the men with syphilis was  $52.53 \pm 0.36$  years, which is significantly lower than that of the nonsyphilitic men. In contrast to this finding, the mean age of syphilitic women was  $51.95 \pm 1.01$  years, actually no different from the mean value for the nonsyphilitic women. In these cumulative observations it appears that the average span of life of the syphilitic man was shortened by about two years, as compared with that of the nonsyphilitic man, although the woman with syphilis had an average duration of life no shorter than her nonsyphilitic sister. Sex apparently exerted no significant influence on the average age at death of the syphilitic person, since both men and women with syphilis had a mean age of about 52 years.

Great care must be exercised in drawing conclusions from the mean age at death, because such values are easily affected by variations in the age distribution of different groups. For this reason the analysis shown in table 4 and charts 2 and 3 is presented. About 9 per cent of the deaths in the nonsyphilitic male population over 20 years of age occurred during the third decade of life, as compared

19 Schrek, R. Further Quantitative Methods for the Study of Transplantable Tumors. The Growth of R39 Sarcoma and Brown-Pearce Carcinoma, *Am J Cancer* 28:345, 1936.

with less than 2 per cent of the deaths among syphilitic men. Approximately 50 per cent of the deaths in the nonsyphilitic group occurred between 30 and 59 years of age, while 70 per cent of the syphilitic deaths took place in this age class. Finally, about 20 per cent of the nonsyphilitic men survived beyond the age of 70, in contrast to less than 7 per cent of those with syphilis.

A similar analysis of the data for women gives essentially similar results. About 15 per cent of the deaths among nonsyphilitic women took place in the third decade of life, as compared with only 5 per cent of the syphilitic deaths. Approximately half of the nonsyphilitic women died between 30 and 60 years of age, as compared with two thirds of the syphilitic women. Moreover, about 20 per cent of the nonsyphilitic women survived beyond the age of 70, in contrast to only 9 per cent of the syphilitic women.

It is not our intent that these curves be interpreted as being typical of syphilis in this country. A composite curve was drawn instead of individual curves for each author in order to smooth the irregularities that would appear in the limited observations in the individual reports. These composite curves should be compared with each other as regards syphilitic and nonsyphilitic persons. From this viewpoint, and in the combined experience of the authors cited, the syphilitic man

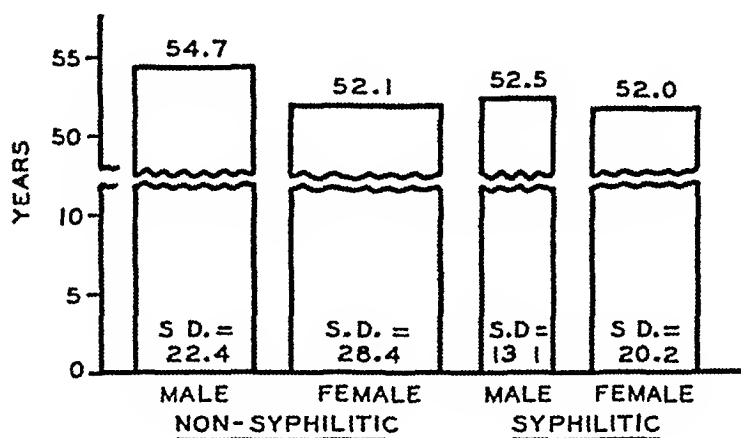


Chart 4—Mean age and standard deviation for men and women with and without lesions of syphilis at autopsy. S. D. indicates standard deviation.

living into the forties and the syphilitic woman living into the fifties had a shorter life span than their nonsyphilitic brother and sister. It should be noted that each of the curves in charts 2 and 3 is represented by a straight line, indicating a normal frequency distribution.

One other observation with regard to age is of significance. This refers to the degree of variability of the frequency distributions for the syphilitic and nonsyphilitic men and women. In charts 2 and 3 the slope of the curve indicates variability, the steeper the slope the greater the variability. In chart 4 variability is proportional to the width of the bars. In both sexes the age distribution of the syphilitic group is less variable than that of the nonsyphilitic group, and this difference is highly significant. (The standard deviation equals  $22.4 \pm 0.10$  for nonsyphilitic men and  $13.07 \pm 0.27$  for syphilitic men, the difference being  $9.33 \pm 0.27$ , and  $t, 35$ . The standard deviation equals  $28.4 \pm 0.16$  for nonsyphilitic women and  $20.2 \pm 0.23$  for syphilitic women, the difference being  $8.2 \pm 0.28$ , and  $t, 30$ .) The extremes of age between 20 and 70 are lopped off in the syphilitic groups as compared with the nonsyphilitic. Fewer young and fewer old subjects are found in the syphilitic than in the nonsyphilitic population.

The incidence of syphilis diagnosed at autopsy in relation to age and sex is shown in table 5. The highest incidence of syphilis occurred among men in the fifth decade and among women in the sixth decade, but in each decade syphilis was more frequent among men than among women. A possible but completely improbable explanation for the high incidence of syphilis in Warthin's, Hala's and Ophuls' populations is here indicated. If their autopsy populations were composed entirely of Negro men aged 40 to 50, a plausible explanation for the high incidence of syphilis which they reported might be offered. There is internal evidence in their publications, however, to discredit this hypothesis, and other explanations must therefore be sought.

#### DIAGNOSTIC CRITERIA

It is generally recognized that the criteria for the pathologic diagnosis of syphilis are not definitive. Before the advent of Warthin's "The New Pathology of Syphilis" a relative uniformity of criteria did exist. These criteria were and still are to be found in the standard textbooks here and abroad. Outside of the United States and Canada, Warthin's influence has failed to make the impression which, on this continent at any rate, has resulted in the broadening of the pathologic

TABLE 5—*Incidence of Syphilitic Lesions at Autopsy in Men and in Women According to Age, by Decades (Summated from Reports of Bell, Fraates, Koppisch, Melchior and Teodor)*

Age	Total Number		Syphilitic Persons			
	Men	Women	Number		Per Cent	
			Men	Women	Men	Women
20-29	2,251	2,212	22	21	0.98	0.94
30-39	2,529	2,359	173	62	6.84	2.62
40-49	4,817	2,479	338	95	7.43	3.82
50-59	5,751	2,489	381	106	6.62	4.26
60-69	5,656	2,796	272	80	4.80	2.86
70+	4,477	2,910	86	36	1.92	1.24
Total	25,484	15,245	1,292	400	5.07	2.62

concept of syphilis. This influence is more readily appreciated when the reports on lesions of individual organs, such as the stomach, testicle, kidney, liver and adrenal glands, are considered than when the more general reports, such as those of table 1, are reviewed. It must, however, be stated that before Warthin's publications appeared, the specific nature of the syphilitic lesion was the subject of much controversy and in fact was the very basis which made Warthin's interpretation possible.

Because of the paucity of comparable anatomic studies, and the total lack of uniformity of criteria, the entire subject of the pathology of syphilis is a maze in which both the expert and the not-so-expert are frequently lost. When the incidence of syphilis of the liver in comparable populations ranges from 3.3 per cent to 33.4 per cent and when one author designates all hepatic syphilis as hepatic lobatum, while another diagnoses only 3.3 per cent as such, it is obvious that complete confusion in terminology and interpretation of lesions exists. It thus becomes apparent that of primary importance in an evaluation of statistics of this type are the criteria followed by the different observers. Here one finds sufficient variability to account in large part for the divergent results.

Warthin<sup>5</sup> stated

The pathologic diagnosis of syphilis is essentially microscopic. Only in a relatively small number of cases are the gross lesions typical enough to be recognized by the naked eye. A negative diagnosis of syphilis cannot be given with any certainty without a routine

microscopic examination of all organs and tissues, but particularly of the left ventricular wall, the aorta, both its arch and abdominal portion, the testes, pancreas and adrenals

The new pathology of syphilis is based upon the demonstration that the essential tissue lesion of either late or latent syphilis is an irritative or inflammatory process, usually mild in degree, characterized by lymphocytic and plasma cell infiltrations in the stroma particularly about the blood vessels and lymphatics, slight tissue proliferation, eventually fibrosis, and atrophy or degeneration of the parenchyma

This concept is in direct contrast to that of Nickel,<sup>20</sup> who is representative of many of the authors listed in table 1. Nickel's criteria may be freely translated as follows

Only definite anatomic syphilis, i. e., syphilitic vascular disease, syphilis of the central nervous system, syphilis of the bone, gumma and interstitial hepatitis of the newborn, was included. Presumptive evidence of syphilis was not considered, i. e., orchitis fibrosa, cicatricial atrophy of the tongue and so-called syphilitic cirrhosis, nor was a positive Wassermann reaction

Nickel specifically disregarded orchitis fibrosa, lingua glabra and "so-called syphilitic cirrhosis" of the liver, nor did he mention changes in the pancreas and adrenals, as did Warthin. The latter also emphasized testicular fibrosis, and, in fact, Weller<sup>21</sup> who was for many years associated with Warthin, made the following statement: "In our opinion, testicular lesions rank second only to those of the aorta as to value in recognition of latent (nongummatous) visceral syphilis." The contrast between Warthin and Nickel is readily apparent and is so sharply drawn that their conclusions cannot be fairly compared.

Symmers employed essentially the same criteria as Nickel but differed from him in the interpretation of specific lesions. For example, Symmers found that 33.4 per cent of his syphilitic subjects presented hepatic syphilis of both the hepatic lobatum type and the cirrhotic form, while Nickel specifically excluded from his series subjects with so-called syphilitic cirrhosis. Moreover, Symmers included subjects with the "presumptive changes of syphilis," such as orchitis fibrosa and lingua glabra, in his series. In spite of this, it is noteworthy that there is no significant difference between the 7 per cent incidence reported by Nickel and the 6 per cent observed by Symmers.

Hala, apparently a disciple of Warthin, accepted as syphilitic any subject to whom two of the following criteria applied: (1) a clinical history of antecedent infection or clinical evidence of existing syphilis, (2) a positive Wassermann reaction, (3) the observation of typical gross lesions at autopsy and (4) histologic evidence of syphilis.

It is evident that the first two criteria are not anatomic, and since the number of subjects admitted to the series on this basis is not stated, the comparative value of the entire work is placed in jeopardy. Moreover, the freedom of action which the four criteria gives to the author is evidenced by the statement that "subpleural aggregations of small round cells (miliary gummata?)" were noted in a considerable number of persons with syphilis, all of whom had pulmonary tuberculosis and the large majority of whom died of tuberculosis.

Frates included not only persons with anatomic lesions but those with a positive Wassermann reaction or a clinical history of infection. However, these two groups are so well differentiated that it was possible to recalculate the author's findings and incorporate in table 1 only those cases in which there were definite anatomic lesions of syphilis.

20 Nickel, H. Statistische Untersuchungen über die Häufigkeit der Lues am Obductionsmaterial, *Klin. Wchnschr.* **15** 121, 1936.

21 Weller, C. V. The Visceral Pathology in Human Treponematosis, *Am. J. Syph., Gonorr. & Ven. Dis.* **21** 357, 1937.

While Ophuls did not enumerate criteria in a formal statement, one may deduce them from his paper. For example, he included a subject with "myocardial syphilis on the basis of clinical history and course." He included another with chronic diffuse interstitial inflammation of pulmonary tissue with cor pulmonale, designated as syphilitic. Twenty per cent of Ophuls' syphilitic patients had syphilitic hepatic disease, in contrast to Warthin's 30 per cent and Nickel's 4.23 per cent. Ophuls also included patients with orchitis fibrosa but added, "They may be syphilitic." The remainder of the authors followed in general the criteria described by Nickel.

The reports show considerable variation with respect to the routine use of microscopic examination of tissues, or of gross examination alone, in the anatomic diagnosis of syphilis. There is, however, compelling evidence that this variation is less important in accounting for the difference in frequency rates than is the variability in diagnostic criteria. Among authors relying entirely or almost entirely on gross examination in reaching a diagnosis of syphilis are Teodori, Frates, Symmers, Manohar and Ophuls. The first three reported a frequency of 4.8 per cent, 5.1 per cent and 6.3 per cent, respectively. These are all comparable results. The last two recorded rates two and three times as great, that is, 15.8 per cent and 11.2 per cent. It appears from these reports that there is distinct lack of uniformity in the interpretation of the gross tissue changes produced by syphilis.

The same variability in diagnostic criteria is apparent in the reports based on microscopic evidence of syphilis. These include the reports of Guldberg<sup>22</sup> (5.8 per cent), Koppisch (11.3 per cent), Hala (21.1 per cent) and Warthin (29.5 per cent). The first of these authors found no greater incidence of syphilis through the study of routine histologic preparations than did Teodori, Frates or Symmers, all of whom relied predominantly on gross examination alone. The disparity between Guldberg's observations, on the one hand and Warthin's, on the other, is so striking as to suggest that it results not so much from a real difference in the incidence of syphilis in the two populations as from significant differences in the diagnostic criteria followed by the two investigators.

The conclusion is warranted that there is a clear need for a restatement of the morphologic changes, both gross and microscopic, which result from syphilitic infection. This is especially true with regard to the histologic alterations described by Warthin as definitive, and this aspect of the problem we plan to pursue in a future study. Precise evaluation of the anatomic changes of syphilis in terms of morbidity and mortality will depend primarily on the standardization of diagnostic criteria and on the general adoption of a uniform nomenclature.

#### SUMMARY

A critical review of the available literature on the incidence of syphilitic infection in adults as determined by various autopsy studies is presented.

The frequency of syphilitic changes encountered at autopsy among persons over 20 years of age varied from a low of 2.6 per cent to a high of 29.5 per cent. The average for seventeen different reports was 8.8 per cent. The average based on the summated autopsy populations of the seventeen reports was 5.5 per cent.

Although syphilis was demonstrably more frequent in the Negro than in the white race, the racial composition of the different populations did not appear sufficient to account for the diverse results.

<sup>22</sup> Guldberg, G. Ueber Sektionsbefunde bei Syphilitikern, Arch. f. Dermat. u. Syph. 166: 730, 1932.

Exact information on the social and economic status of the several populations was lacking, but this status did not appear to play an important role in explaining the widely divergent findings.

A higher proportion of men and a lower proportion of women showed evidence of syphilis at autopsy than could be expected on the basis of the proportions of the sexes in the combined populations. The mean age of the men over 20 with syphilis in reports giving age and sex data was 52.1 years, or one and a half years younger than the mean age for nonsyphilitic men. This difference was significant. Women over 20 years of age with syphilis had an average age of 52 years, essentially the same as the mean age of the nonsyphilitic women. Only 7 per cent of the syphilitic men and 9 per cent of the syphilitic women survived the age of 70, in contrast to 20 per cent of the nonsyphilitic men and women. The highest incidence of syphilis occurred among men in the fifth decade and among women in the sixth decade, but in each decade syphilis was more frequent among men than among women. It could not be conclusively demonstrated that these findings with respect to age and sex were responsible for the widely divergent estimates of the incidence of syphilis at autopsy.

The great variability in the diagnostic criteria both gross and microscopic, employed by different observers was appraised, and the need for uniformity of nomenclature and standardization of criteria was stressed. It was suggested that the major factor accounting for the great variability in the frequency of syphilitic lesions encountered at autopsy was precisely this lack of uniformity in the diagnostic criteria employed by the several investigators.

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# NITROGEN EQUILIBRIUM AND REGENERATION OF SERUM PROTEIN

FOLLOWING INTRAVENOUS USE OF AMINO ACIDS

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Attention to nitrogen balance and the level of the blood proteins has of late years come to be recognized as an important part of preoperative and postoperative care<sup>1</sup> in cases of diseases of the liver and biliary tract,<sup>2</sup> of severe burns<sup>4</sup> and of shock.<sup>5</sup> A variety of substances have been used as sources of nitrogen. In shock, the necessity of obtaining immediate increase in osmotic pressure of the serum to prevent hemoconcentration makes human plasma and serum of undisputed importance since simply by giving them one places proteins in circulation. The protein is in addition available for use by the body for maintaining nitrogen equilibrium and building new serum protein. The cost of collection and preparation of human plasma and serum is considerable and for this reason Wangensteen and his co-workers<sup>6</sup> have attempted to use beef plasma as a substitute, with some degree of success. Solutions of hydrolyzed casein may also be prepared relatively cheaply, and since they are capable of being metabolized by the body<sup>7</sup> and furnish material with which serum proteins may be built, they may be used to advantage as a source of nitrogen. But because amino acids exert little if any osmotic pressure in solution they obviously cannot replace whole blood or serum when an immediate effect on blood volume is required and are to be regarded as easily usable sources of nitrogen.

Elman and Wiener<sup>8</sup> have shown that plasma administered intravenously replenishes circulating proteins, but they stated that it must be completely broken down into simple amino acids and subsequently resynthesized before utilization. For this reason, they expressed the belief that amino acids resulting from the

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1 (a) Jones, C M, and Eaton, F B. Postoperative Nutritional Edema, *Arch Surg* **27** 159 (July) 1933. (b) Stengel, A, Jr, and Ravdin, I S. The Maintenance of Nutrition in Surgical Patients, with a Description of the Orojejunal Method of Feeding, *Surgery* **4** 511, 1939. (c) Ravdin, I S, Stengel, A, Jr, and Prushankin, M. The Control of Hypoproteinemia in Surgical Patients, *J A M A* **114** 107 (Jan 13) 1940.

2 Ravdin, I S. The Protection of the Liver from Injury, *Surgery* **8** 204, 1940.

3 Jones, C M. Treatment of Biliary-Tract Disease, *New England J Med* **224** 509, 1941.

4 (a) Elman, R. The Therapeutic Significance of Plasma Protein Replacement in Severe Burns, *J A M A* **116** 213 (Jan 18) 1941. (b) McClure, R D. The Treatment of a Patient with Severe Burns, *ibid* **113** 1809 (Nov 11) 1939.

5 Bond, D D, and Wright, D G. Treatment of Hemorrhage and Traumatic Shock by Intravenous Use of Lyophile Serum, *Ann Surg* **107** 500, 1938.

6 Wangensteen, O H, Hall, H, Kremen, A, and Stevens, B. Intravenous Administration of Bovine and Human Plasma to Man. Proof of Utilization, *Proc Soc Exper Biol & Med* **43** 616, 1940.

7 Shohl, A T, Butler, A M, Blackfan, K D, and MacLachlan, E. Nitrogen Metabolism During the Oral and Parenteral Administration of the Amino Acids of Hydrolyzed Casein, *J Pediat* **15** 469, 1939.

8 Elman, R, and Wiener, D O. Intravenous Alimentation, *J A M A* **112** 796 (March 4) 1939.



hydrolysis of casein constitute at least as good material for building proteins as whole serum or plasma. Recently, Madden and co-workers<sup>9</sup> have shown experimentally that casein digests are utilized for producing new plasma protein in dogs made hypoproteinemic by plasmapheresis. With a suitable casein digest, the same response was elicited by either intravenous or oral administration, and nitrogen balance was maintained for considerable periods. Since the initial report of Elman and Weiner<sup>8</sup> on the use of hydrolyzed casein as a substance suitable for intravenous use in human beings, many other investigators<sup>10</sup> have contributed to the literature on the subject.

For the past year and a half, the effects of the use of solutions of amino acids on a variety of hypoproteinemic states and on maintenance of nitrogen balance have been studied in this hospital. The substance of this report is based mainly on the results obtained in 5 of a group of 20 patients who received amino acids intravenously. These 5 were studied in sufficient detail to permit drawing conclusions concerning their ability to use the amino acids for maintenance of nitrogen balance or to regenerate serum protein.

### METHODS

The amino acids<sup>11</sup> used were prepared in concentrations of 5, 15 or 20 per cent in rubber-stoppered glass bottles, from which they were transferred to infusion flasks for intravenous administration, as needed. The maximal rate at which infusions were allowed to proceed was about 180 cc per hour. The 15 and 20 per cent solutions were, however, always diluted to twice or three times their original volumes. Reactions following infusions did not occur. Occasionally, when infusion rates exceeded 200 cc per hour, sensations of warmth and, rarely, of nausea were experienced. Reduction of the speed of flow usually relieved these symptoms promptly. The more cooperative patients became adept in regulating their own infusions. When large amounts of amino acids were given daily, it was found better to divide the dose into two or more parts, especially if the regular intake of food was not interrupted.

Determinations of nitrogen were carried out by the micro-Kjeldahl procedure. Serum albumin was estimated by the method of Campbell and Hanna.<sup>12</sup>

### REPORT OF CASES

**CASE 1**—C. A. A., a 19 year old man, a factory employee, was admitted to the hospital on Sept 6, 1941 complaining of weakness and diarrhea. He had been well until November 1939, when he suffered an attack of severe diarrhea, which was diagnosed as ulcerative colitis; he was treated at home by his physician. A spontaneous remission of symptoms occurred. In July 1940 recurrence of severe colic, diarrhea, rectal bleeding and loss of weight caused his admission to the Third (New York University) Medical Division, Bellevue Hospital, where a second remission of symptoms took place after about two months. A month later he was transferred to Welfare Hospital for Chronic Diseases.

9 Madden, S. C., Zeldis, L. J., Hengerer, A. D., Miller, L. L., Rowe, A. P., Turner, A. P., and Whipple, G. H. Casein Digests Parenterally Utilized to Form Blood Plasma Protein, *J. Exper. Med.* **73** 727, 1941.

10 (a) Farr, L. E., and MacFadyen, D. A. Hypoaminoacidemia in Children with Nephrotic Crises, *Am. J. Dis. Child.* **59** 782 (April) 1940. (b) Cox, W. M., Jr., and Mueller, A. J. Nitrogen Retention on Casein Digests, *Proc. Soc. Exper. Biol. & Med.* **42** 658, 1939. (c) Messinger, W. J. Serum Protein Regeneration Following Use of Amino Acids in Nephritis (Nephrotic Stage), *ibid.* **47** 281, 1941. (d) Shohl, Butler, Blackfan and MacLachlan.<sup>7</sup>

11 The amino acids used in these studies were prepared by acid hydrolysis of casein, fortified with 1 per cent tryptophan. Eighty per cent of the total nitrogen is said to be present in the form of amino acid nitrogen. These amino acids were supplied by Frederick Stearns & Co.

12 Campbell, W. R., and Hanna, M. I. Albumin, Globulins, and Fibrinogen of Serum and Plasma, *J. Biol. Chem.* **119** 15, 1937.

On examination, the patient appeared ill. There was marked loss of subcutaneous fat, the mucous membranes were pale and the skin had a sallow appearance. Diffuse abdominal tenderness and increase of peristalsis were present, otherwise there were no abnormalities.

The erythrocytes numbered 2,500,000 and the leukocytes 8,600 per cubic millimeter of blood. The hemoglobin amounted to 6 Gm per hundred cubic centimeters. Study of blood smears revealed a moderate hypochromic, microcytic anemia and a normal leukocyte differential count. The Wassermann reaction was negative. The value for serum proteins was 5 Gm per hundred cubic centimeters, of which 3 Gm was albumin. Values for blood sugar, urea nitrogen, calcium and phosphorus were normal. No abnormalities were found on examination of the urine. Roentgenograms of the colon taken after a barium sulfate enema showed absence of haustrations and a smooth contour of the left half of the colon. Sigmoidoscopy revealed pale atrophic mucous membranes studded with many small scars. Numerous fresh bleeding points in the upper part of the rectum were also observed. Fresh

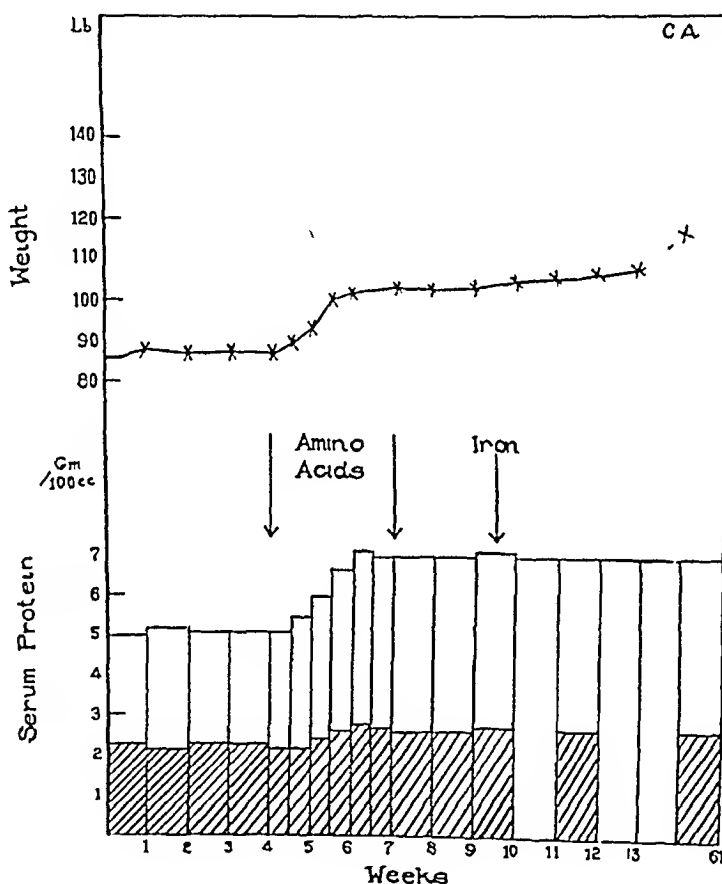


Chart 1 (case 1) —The weight curve and level of serum proteins are shown for periods before, during and after daily administration of 500 cc of a 5 per cent solution of amino acids. The height of each column at the bottom of the chart represents the level of total serum proteins during the period shown, cross-hatched portion, serum globulin, the clear portion, serum albumin, except during the eleventh and thirteenth weeks, when only the total protein was measured.

stool removed through the sigmoidoscope contained some red blood cells and many epithelial cells but no pathogenic organisms or parasites.

The patient was placed at complete rest in bed. A bland diet rich in carbohydrate, containing 110 Gm of protein daily and supplemented by parenteral vitamins was given. Small transfusions were administered frequently. Although he was afebrile and was passing only two formed stools containing but few red blood cells daily, he failed to gain weight and anemia persisted. A course of emetine hydrochloride was administered, without appreciable effect. On three occasions the patient suffered a recurrence of diarrhea (eight to ten loose stools daily) and cramps lasting a few days each. Two of these episodes were related to indiscretions in food, and the third followed a severe pharyngitis. During a period of three months, gain in weight and rise in the level of serum proteins or in the red blood

cell count failed to take place. It seemed reasonable, therefore, to use amino acid solutions as a means of supplying nitrogen.

Daily intravenous infusions of 500 cc of a 5 per cent solution of amino acids, equivalent to 5 Gm of nitrogen, and 5 per cent dextrose solution were given for twenty-one days as a supplement to his regular diet. They were generally given after breakfast and appeared to enhance the subject's appetite. At the end of the first week of this regimen a rise in the level of serum proteins and gain in weight began, and by the end of the third week the serum proteins had reached normal values (chart 1). Subjectively, improvement was marked by the fact that the patient became more hopeful of his eventual recovery. Little change in the red blood cell count or hemoglobin content occurred even after six weeks, and consequently 2 cc of a solution of iron and ammonium citrates (0.5 Gm of iron per cubic centimeter) was injected intramuscularly each day. During the next three weeks the red blood cell count and hemoglobin content rose to 3,900,000 and 118 Gm respectively without, apparently, affecting the level of the serum proteins. Eight months after he had received the amino acids he continued well and the value of the serum proteins remained within the normal range, but a slight degree of anemia was still present.

TABLE 1—*Nitrogen Balance and Level of Serum Proteins (in Case 2) Before and After Operation*

Day	Source of Nitrogen Intake per Twenty Four Hours					Total Intake of Nitrogen per 24 Hr., Gm	Total Output of Nitrogen per 24 Hr., Gm	Nitrogen Balance	Serum Proteins A/G Ratio
	Whole Blood		Amino Acids		Food Nitrogen Gm				
	Cc	Nitrogen, Gm	Cc	Nitrogen Gm					
1						0	3.6	-3.6	3 0/2 8
2						0	3.0	-3.1	
3						0	3.4	-3.4	3 0/2 8
4						0	3.1	-3.1	
5	250	1.1				1.1	2.8	-1.7	3 0/2 8
6	250	1.1	150	3.0		4.1	3.7	+0.4	
7	250	1.1	250	5.0		6.1	5.8	+0.3	3 0/2 9
8	250	1.1	250	5.0		6.1	5.0	+1.1	
9*	500	2.1	500	10.0		12.1	1.7	+10.4	3 2/2 8
10	200	1.0	900	18.0		19.0	11.1†	+5.8	
11	250	1.0	900	18.0		19.0	10.8	+8.2	3 1/2 8
12			900	18.0		18.0	16.9	+1.1	3 0/2 8
13			900	18.0		18.0	13.4	+4.6	
14			750	15.0		15.0	11.6	+3.4	3 1/2 9
15			750	15.0		15.0	10.1	+4.9	3 3/3 0
16			600	12.0		12.0	9.6	+2.4	
17			600	12.0	2.0	14.0	9.4	+4.6	3 4/3 0
18			400	8.0	3.0	11.0	9.1	+1.9	
19			400	8.0	1.0	11.0	9.3	+1.7	
20			200‡	4.0	10.0	14.0	10.2	+3.8	3 4/3 0
21			160‡	2.0	11.0	13.0	10.0	+3.0	
22					16.0	16.0	10.7	+5.3	3 6/3 0

\* Day of operation

† In fifteen hours

‡ Oral amino acids

CASE 2—R. H., a 32 year old white man, was admitted to the hospital on Nov. 16, 1940. He had apparently been well and working as a linesman until March 1938, when he first noticed discomfort in the upper part of the abdomen and eructations. A physician advised him that his symptoms were caused by a peptic ulcer. Several weeks later, chills, weakness and severe abdominal pain forced him to seek hospital care. He had at this time lost 30 pounds (13.6 Kg.). In September 1939 and again in March 1940 the same symptoms recurred accompanied by syncope, and on both of these occasions he was hospitalized. In May 1940, during the fourth admission to the hospital, a large mass was palpated by rectum in the cul-de-sac, and with the help of roentgen examination a diagnosis of regional ileitis was made. Surgical exploration was carried out, and a large mass in the cul-de-sac, made up of lymph nodes, cecum and terminal ileum adherent to the bladder and rectum, was found. Since the process was extensive, it was decided not to attempt removal. Roentgen irradiation of the abdomen was, however, followed by slight diminution in the size of the mass about the rectum. The patient was then transferred to this hospital.

On examination, marked emaciation was evident. The thighs were flexed on the abdomen to relieve abdominal pain. There was a long well healed rectus scar, and the lower portion of the abdomen was protuberant. The liver and spleen were not palpable, and the presence of abdominal fluid was not demonstrated. On rectal examination a moderately tender mass

about the size of a large grapefruit was palpated in the cul-de-sac. The rectum itself was not found to be abnormal by palpation or by proctoscopy. The results of physical examination were in other respects normal.

The erythrocytes numbered 3,400,000 and the leukocytes 7,700 per cubic millimeter of blood and the hemoglobin content was 117 Gm per hundred cubic centimeters. A differential count of the leukocytes showed that 80 per cent of them were polymorphonuclear leukocytes. The Wassermann reaction was negative. The serum proteins ranged between 55 and 58 Gm per hundred cubic centimeters. The values for urea nitrogen, sugar, calcium and phosphorus of the blood were normal. The urine was normal throughout. Neither gross nor occult blood, pathogenic organisms or parasites were found in the stool. The reaction to a tuberculin test (old tuberculin in dilutions of 1:100,000 to 1:1,000) was negative. Repeated Frei tests gave negative reactions. Roentgenograms of the gastrointestinal tract taken after the ingestion of barium sulfate and of the rectum after a barium enema

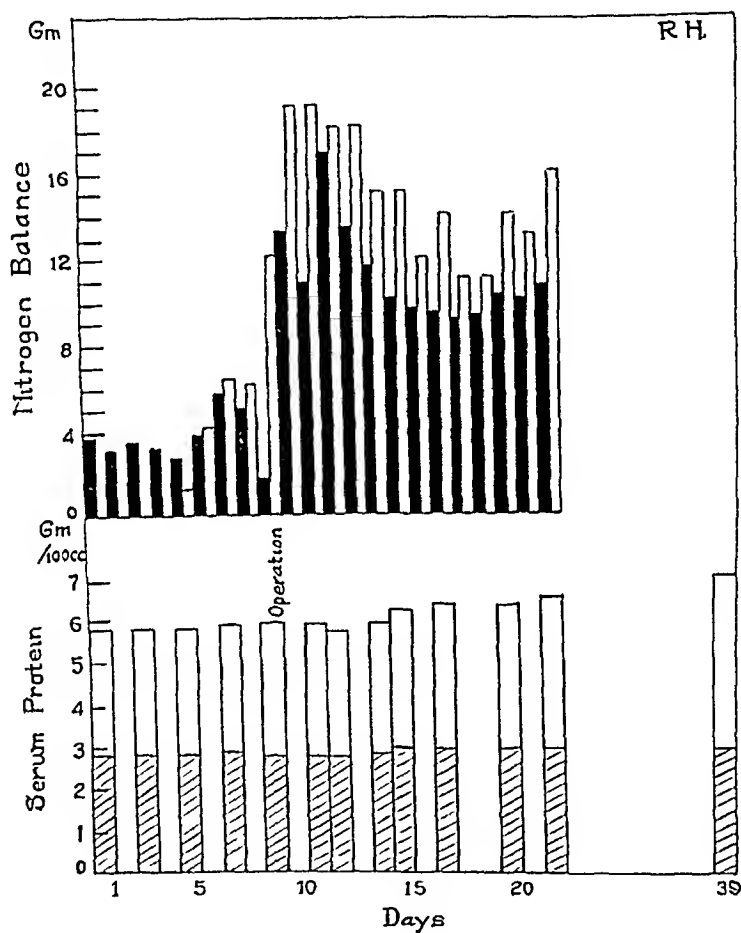


Chart 2 (case 2)—The nitrogen balance and the level of the serum proteins are shown for a nine day period prior to operation and for thirteen days after operation. Each solid black column represents nitrogen output for a twenty-four hour period, while the enclosed clear column, to the right of each black one, indicates the nitrogen intake for the same period. The nitrogen intake on the first four days was zero. The columns representing levels of serum protein are as described for chart 1.

revealed only distended loops of small bowel. On one occasion, the appearance of the roentgenogram suggested the diagnosis of tuberculosis of the cecum.

The patient was placed on a high calory diet rich in protein, carbohydrate and vitamin B complex. Bouts of nausea and vomiting and diffuse abdominal pain accompanied by visible hyperperistaltic waves continued to occur. Temporary relief was usually obtained by the use of atropine, narcotics or Wangensteen drainage. During a period of four months, improvement failed to occur. Since hypoproteinemia persisted, two infusions of 150 cc each of a 15 per cent solution of amino acids (6 Gm of nitrogen) diluted to 450 cc with 5 per cent dextrose solution were given daily for fourteen days, without increase in the serum proteins or improvement in the nutritional state. Because the presence of symptoms and

signs of partial obstruction made surgical intervention appear inescapable, an attempt was made to maintain the patient in nitrogen equilibrium and furnish his caloric requirements entirely by intravenous infusion in order to afford rest to the gastrointestinal tract before operation. For four days preceding operation food was not given by mouth. The only food available was given intravenously in solutions containing 15 per cent amino acids and 10 per cent dextrose and in a few small transfusions of whole blood (table 1). The number of calories furnished by this material generally exceeded 1,500 for each twenty-four hour period. Minerals were supplied by adding concentrated Ringer-Loeke solution to the infusions. The patient volunteered the information that his abdominal pain decreased markedly during this period.

At operation, a large pelvic mass was found in the cul-de-sac. It consisted of loops of ileum, cecum and a considerable amount of acute and chronic inflammatory tissue. The tip of the appendix was, on careful dissection, found to be incorporated in the mass. Gross and microscopic study of the specimen removed at operation failed to decide whether the original condition was a regional ileitis involving the cecum and appendix or an appendical abscess involving the ileum.

For eight days after operation, the patient was, except for small transfusions (table 1), fed parenterally with solutions of dextrose and amino acids. His nutritional state was excellent, judged by prompt healing of his wound, continuous positive nitrogen balance and increase in serum proteins (chart 2). The nitrogen derived from transfusions was calculated from the serum protein content and amount of blood used. Five months after operation, the patient was fairly well. His weight was 141 pounds (64 Kg), and he was earning his livelihood. Serum proteins were within normal limits and at about the level shown on the thirty-ninth day after operation (chart 2).

CASE 3—C. H., a 21 year old white woman, was admitted to the hospital on April 31, 1940, with complaints of generalized edema, headaches and irregularity of the menses. Of interest in her past history were the facts that she had suffered an uncomplicated attack of scarlet fever in childhood and that she had had otitis media necessitating myringotomy at the age of 17.

During the summer of 1937, while traveling in Europe, the patient became ill of a severe infection of the upper respiratory tract, which subsided in about ten days. On her return to this country four months later, puffiness about the eyes and edema of the ankles were noted, and she was told by her physician that she had nephritis. A year later generalized edema appeared. During the three year interval between the onset of the edema and admission to this hospital, the patient felt quite well, although it was learned from the physician's record that large amounts of albumin and numerous formed elements were regularly found in the urine and that hypoproteinemia, hypercholesteremia and anemia were continually present. Arterial pressure was normal.

On examination, the generalized edema and puffiness about the eyes were seen to be marked. The skin was pasty. Slight increase in light reflex of the retinal arteries was noted. The arterial pressure varied between 140 and 160 mm of mercury systolic and 96 and 110 mm diastolic. Examination otherwise showed nothing abnormal.

There were 2,750,000 red blood cells per cubic millimeter and 9 Gm of hemoglobin per hundred cubic centimeters of blood. The leukocytes were normal as to number and variety. The level of sugar in the blood was 86 mg per hundred cubic centimeters, urea nitrogen 28 to 33 mg, total cholesterol 830 to 1,100 mg, total protein 3.94 to 4.8 Gm (albumin about 1.5 Gm and globulin 2.5 Gm), calcium 8.6 mg, phosphorus 5.9 mg and phosphatase 9.2 Bodansky units. The Wassermann reaction of the blood was negative. The basal metabolic rate was -15 per cent. Roentgenograms showed the heart to be enlarged to the left and demonstrated coarse trabeculations of the humeri. The electrocardiogram was normal. Examination of the urine yielded a maximal specific gravity of 1.012. Seven to 10 Gm of albumin was found regularly in each twenty-four hour specimen of urine. The centrifuged sediment under the microscope showed 1 or 2 granular casts per high power field, occasional waxy casts, white blood cells and rare red blood cells. Doubly refractive bodies were shown to be present by the polarizing microscope. Phenolsulfonphthalein excretion was 27.5 per cent in two hours. The standard urea clearance was 38.2 per cent of normal.

The patient was placed on a salt-poor, low fat diet containing 120 Gm of protein and on 1,500 cc of fluid daily. After an observation period of one month, 500 cc of a 5 per cent solution of amino acids with 5 per cent dextrose was administered daily for fourteen days in addition to the regular diet. Total output of urinary nitrogen, including the albumin

nitrogen, was determined daily for seven day periods before, during and after the fourteen day period of treatment. Values for fecal nitrogen and serum protein were obtained frequently. Increase in the level of the serum proteins failed to occur (chart 3), and there was no change in the output of urinary albumin. During the period of study, consumption of the diet was complete. The weight was constant, the hematocrit value did not change, and there was no obvious change in the clinical condition.

The patient was readmitted to the hospital in October 1940, seriously ill with diffuse bilateral bronchopneumonia, shown by physical examination and roentgenograms of the lungs. During the period of acute infection, the total cholesterol level in the blood decreased and the serum proteins increased (chart 4). When she recovered, both values returned to previous levels. The blood pressure on admission was 136 to 160 mm of mercury systolic and 100 diastolic. Renal function as shown by phenolsulfonphthalein excretion and urea clearance had not changed appreciably. In April 1941 the patient was again readmitted for study. The albumin portion of the serum proteins was for the first time noted to be greater than the globulin (chart 4). Since this time, frequent observation in the clinic shows that the blood pressure has been increasing (systolic level at the time of writing 156 to 164 and diastolic 110 mm of mercury), while edema and body weight have been decreasing. The degree of anemia is unchanged. The urea nitrogen content of the blood has risen to 54 mg per hundred cubic centimeters and the level of the serum proteins to 6 Gm, with albumin 3.3 Gm and globulin 2.7 Gm. The total cholesterol content of the blood has decreased to 384 mg per hundred cubic centimeters. Renal function as measured by the standard urea clearance has fallen steadily to 25 per cent of normal, and phenolsulfonphthalein excretion has diminished to 21 per cent in two hours (chart 4). Doubly refractive bodies are no longer demonstrable in the urine. The albumin content of twenty-four hour specimens of urine now ranges from 3 to 5 Gm per hundred cubic centimeters.

CASE 4—J. C., a 41 year old white man, was admitted to the hospital on April 4, 1940, with the chief complaint of swelling of the legs, he left the hospital against advice two months later and was readmitted on August 4, during which admission the present study was begun. He suffered an attack of scarlet fever in childhood and had gonorrhea at the age of 17 and had been subject to heroin (diacetylmorphine) addiction since the age of 21. The present illness began in 1938, with edema of the ankles, gradually progressing to anasarca within two months. On his admission to a hospital at that time, it was noted that the urine showed a 4 plus reaction for albumin and contained occasional red blood cells and casts and that the concentration of serum proteins was low (3.5 Gm per hundred cubic centimeters), with albumin and globulin present in equal quantities.

On examination, a poor state of nutrition and pallor were obvious. The systolic blood pressure varied from 130 to 160 and the diastolic from 94 to 104 mm of mercury. Slight increase of the light reflex of the retinal arteries was present. Numerous pigmented pitted scars of the skin of the extremities, trunk and abdomen were said by the patient to be the sites of injections of the narcotic during the last fifteen years or more. Examination otherwise showed nothing abnormal.

The red blood cells numbered 2,800,000 and the leukocytes 7,300 per cubic millimeter, and 11 Gm of hemoglobin was present in each hundred cubic centimeters of blood. The values for sugar, calcium and phosphorus in the blood were normal. The blood urea nitrogen varied from 26 to 42 mg per hundred cubic centimeters, the serum proteins from 4 to 4.8 Gm, the albumin fraction from 2.4 to 2.8 Gm and the total serum cholesterol from 450 to 600 mg. The Congo red absorption test was not indicative of amyloid disease. The Wassermann reaction of the blood and the spinal fluid was negative. Examination of the urine showed a maximal specific gravity of 1.014, an albumin content of 6 to 12 Gm in twenty-four hours and absence of reducing agents. Microscopic examination of centrifuged sediment regularly showed occasional granular and hyaline casts, a few white blood cells and rare red blood cells. Doubly refractive bodies in the urine were frequently demonstrable. The standard urea clearance was 28 per cent of normal, and the phenol-sulfonphthalein excretion was 20 per cent in two hours.

The patient was placed on a salt-poor, low fat diet, containing 120 Gm of protein. His fluid intake was regulated at 1,500 cc in twenty-four hours. From 15 to 30 mg of morphine sulfate was necessary five times daily to control the symptoms of addiction, and all efforts to stop use of the drug failed. Generally, he consumed the major portion of his diet but occasionally complained of anorexia and lassitude. Additional amounts of protein and iron given orally did not affect the hypoproteinemia or anemia. After a preliminary period of observation (one month) daily intravenous injections of 180 cc of 20 per cent solution of amino acids<sup>11</sup> diluted with an equal quantity of distilled water were

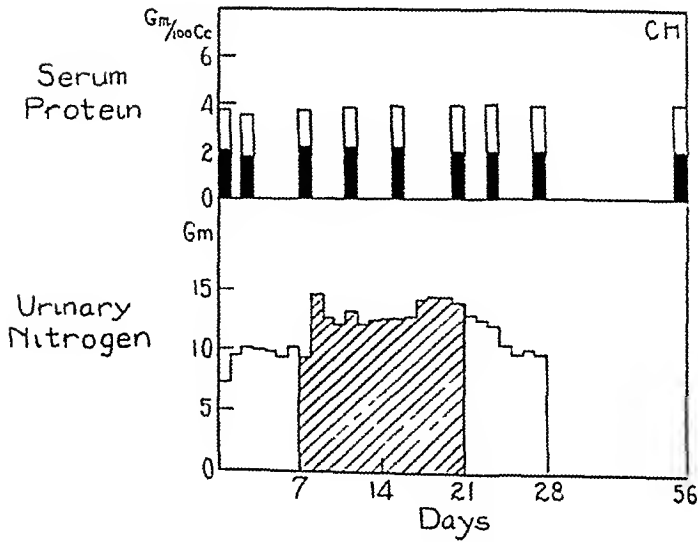


Chart 3 (case 3) —The level of the serum proteins and the urinary nitrogen excretion are shown for periods before, during and after the intravenous administration of amino acids. The light portion of the columns which represent total serum proteins indicates the level of serum albumin. The urinary nitrogen excreted during each twenty-four hour period is shown in blocks at the bottom of the chart. The cross-hatched area indicates the period during which 500 cc. of a 5 per cent solution of amino acids was injected daily. Significant change in the level of serum proteins did not occur.

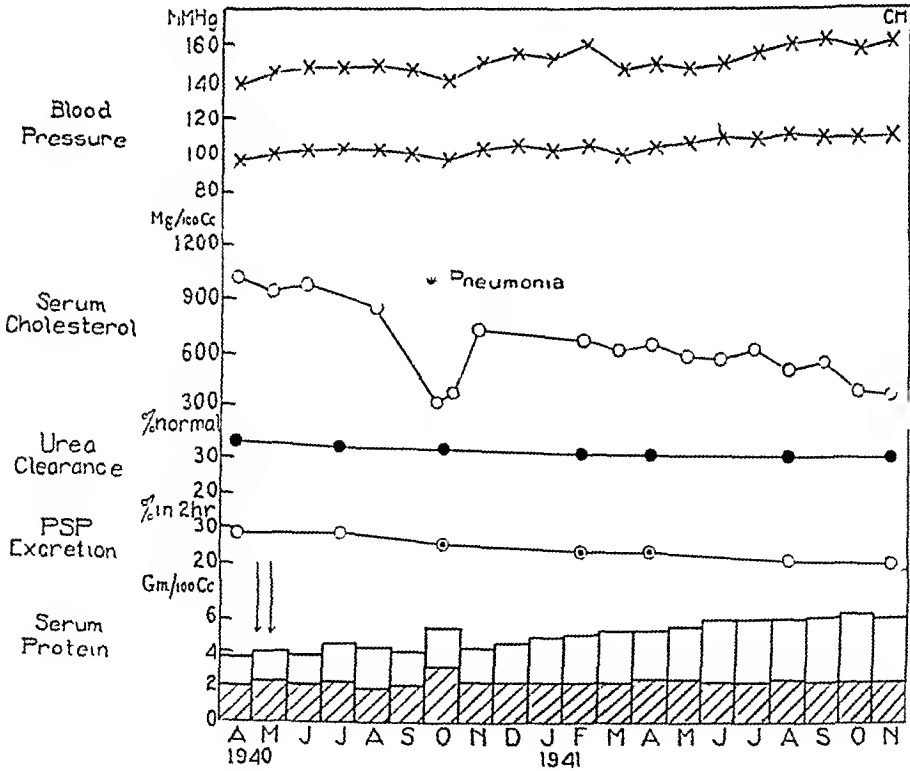


Chart 4 (case 3) —Pertinent data obtained during a twenty month period of observation. Progressive increase in blood pressure is accompanied by decrease in lipemia and renal function. The arrows indicate the period of intravenous amino acid therapy (detail shown in chart 3). Of interest are the abrupt decrease in the cholesterol values and the increase of the globulin fraction of the serum protein during the period of acute febrile illness.

given for eighteen days in addition to the regular diet. Each 100 cc of undiluted amino acids contained 2 Gm of nitrogen. The total output of urinary nitrogen, including albumin, was measured for periods of one week before, during and after the period of administration of the amino acids. Values for fecal nitrogen and serum protein were obtained frequently. After the series of injections of amino acid solutions was completed, a small but definite rise in proteins was noted and the level continued to rise, reaching a peak thirty-six days later (chart 5). The increase in the serum protein level occurred chiefly in the albumin fraction. During the next three months, the serum proteins fell slowly to the previous level and the patient became listless eating his diet only on constant persuasion.

The patient was then restudied under the same conditions except that larger amounts of amino acids were administered. Three hundred cubic centimeters of 15 per cent (2 Gm of nitrogen per hundred cubic centimeters) solution diluted with an equal amount of water was given daily for sixteen days. During the first week of administration, a perceptible rise in serum proteins was noted (chart 5) and the increase continued to a peak of 5.9 Gm per hundred cubic centimeters twelve days after cessation of therapy. The increase again occurred in the albumin fraction. During both periods of therapy there was fairly complete consumption of diet, body weight and hematocrit values were constant. During the latter part of the second period of therapy the patient stated that he thought he could

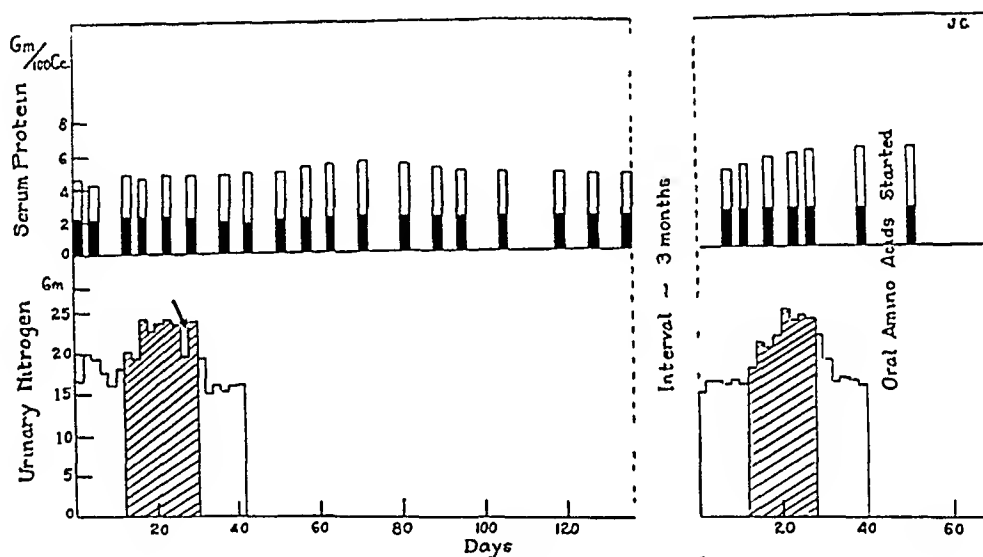


Chart 5 (case 4)—The level of the serum protein and the urinary nitrogen output are shown for periods before, during and after the intravenous administration of amino acids. The light portion of the columns which represent total serum proteins indicates the level of serum albumin, the solid black, serum globulin. The urinary nitrogen excreted during each twenty-four hour period is shown in blocks at the bottom of the chart. The cross-hatched areas indicate the periods during which 180 cc of a 20 per cent solution and 300 cc of a 15 per cent solution of amino acids respectively were given daily. During a two day period the administration of amino acids was omitted, the arrow points to the drop in urinary nitrogen.

diminish his daily morphine requirements, and at the end of the period he voluntarily ceased its use. As far as can be judged, he has not reverted to its use again. He was discharged from the hospital on June 15, 1941 and has been periodically observed in the clinic.

Since the patient's condition appeared excellent, it was decided to test whether serum protein levels might be maintained by the oral administration of the same preparation of amino acids used intravenously. He has therefore ingested 300 cc of a 15 per cent solution in addition to his regular diet every two days ever since, without difficulty. Five months after discharge his serum proteins were still at a level of 5.8 to 6 Gm per hundred cubic centimeters. Arterial pressure, serum cholesterol, phenolsulfonphthalein excretion and urea clearance values changed but little (chart 6). The urine still showed a maximal specific gravity of 1.014, with the albumin content and the variety of formed elements in the sediment unchanged. The patient seems to be in fair health and has no complaints except constant slight edema of the ankles. The anemia has persisted. For the first time in three years, he is gainfully employed.



CASE 5—L L, a 60 year old Norwegian, a former seaman, was admitted to the neurologic service on Aug 6, 1939 because of difficulty in walking for the past fifteen years and increasing dysarthria for nine years. The only seemingly relevant facts in the history were that he had gonorrhea and a chancre in his youth.

On examination, the patient appeared poorly nourished and pale. The retinal arteries exhibited arteriosclerotic changes. The tongue deviated to the right on protrusion. The heart and lungs were essentially normal on both physical and roentgen examination. The arterial pressure was 100 systolic and 60 diastolic. The abdomen was normal, but muscular tone was poor. The peripheral arteries were beaded and tortuous wherever palpable. Neurologic signs pointed to diffuse involvement of pyramidal and cerebellar tracts and to moderately advanced mental deterioration. The extremities showed atrophy of the muscles. Edema was not present.

The number of erythrocytes varied from 3,800,000 to 4,000,000 per cubic millimeter. Each 100 cc of blood contained 11 to 12 Gm of hemoglobin. The leukocytes numbered 8,200 per cubic millimeter, of which 70 per cent were polymorphonuclear leukocytes and 30 per cent lymphocytes. The urine was normal. The Wassermann reaction of both blood

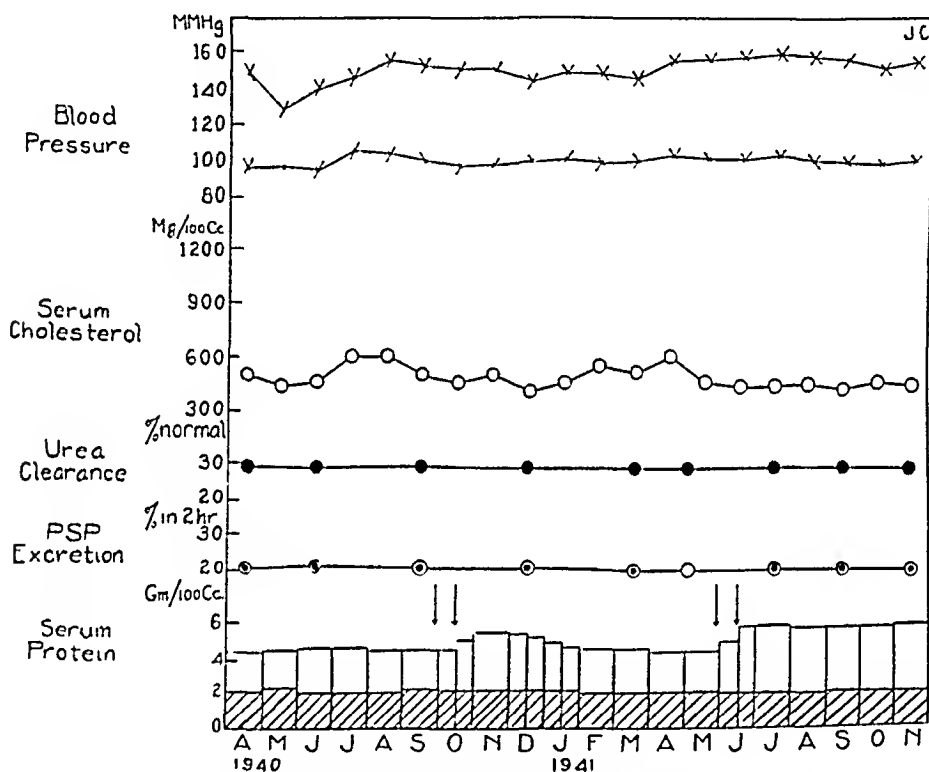


Chart 6 (case 4)—Pertinent data obtained over a twenty month period of observation. Few changes are noted except in the values for serum protein. The height of each column at the bottom of the chart represents the average of three or more measurements of total serum proteins obtained during each month, the cross-hatched areas, serum globulin, and the clear portion, serum albumin. Two sets of arrows indicate the intervals during which amino acids were given intravenously (details shown in chart 5). Increases in serum protein follow both periods of therapy and have been maintained after the second period by the oral administration of amino acids.

and spinal fluid was negative, and the colloidal gold curve of the spinal fluid was normal. Total serum proteins never exceeded 48 Gm per hundred cubic centimeters while the subject was under observation. The albumin content of the serum was regularly 3 Gm per hundred cubic centimeters. Values for blood sugar and urea nitrogen, total cholesterol and cholesterol esters were always within normal limits.

The patient's difficulties were ascribed chiefly to cerebral arteriosclerosis. Occasional febrile episodes probably due to ill defined areas of bronchopneumonia occurred. Frequent periods of complete anorexia, sometimes necessitating gavage, and lack of sufficient protein intake were thought to be factors contributing to the hypoproteinemia. On three separate occasions, during periods of complete anorexia, infusions of 500 cc of 5 per cent amino

acids with 5 per cent dextrose solution were followed by immediate return of appetite and request for food. Infusions of 5 per cent dextrose solution alone did not secure this response. He was then given 500 cc of 5 per cent solutions of amino acids (5 Gm of nitrogen) with 5 per cent dextrose daily, intravenously, in addition to his regular diet, containing 100 Gm of protein, in an effort to raise the level of the serum protein. Two weeks of daily infusions of amino acids failed to raise the level of the serum proteins.

The patient died of an intercurrent pneumonic infection four months after the period of observation. Postmortem examination of the brain substantiated the diagnosis of cerebral arteriosclerosis with involvement of pyramidal and cerebellar structures. The lungs exhibited numerous small areas of consolidation. The state of the liver was, of course, of especial interest, since one obvious reason for failure to regenerate serum proteins is impairment of that function of the liver which is responsible for their elaboration. It weighed 600 Gm and appeared brownish red, and its surface was finely granular. On section, lobulation appeared prominent, and the parenchyma had a peculiar dull brown appearance. Microscopically, the lobules of the liver were surrounded by fine strands of connective tissue and scattered lymphocytes. The hepatic cells were small and in some instances vacuolated. Vacuolation was shown by the use of special stains to be due neither to fat nor to glycogen. The significance of these observations will be discussed.

#### COMMENT

The observation in 1 case (case 2) that solutions of amino acids administered intravenously can maintain nitrogen equilibrium (chart 2) when these substances are the only source of nitrogen available confirms previous reports by other workers<sup>13</sup>. It is probable that when quantities as large as 900 cc of a 15 per cent solution are administered daily (case 2) appreciable amounts may be lost in the urine, but the continuous positive nitrogen balance achieved postoperatively in case 2 makes it evident that a large proportion of the acids was utilized. Particular attention is directed to the large output of nitrogen in this case in the days immediately following operation. Although Elman<sup>13a</sup> has recently emphasized the fact that the occurrence of this phenomenon is a frequent postoperative event, its importance with regard to replacement therapy has not been generally appreciated.

Increase in serum proteins following the intravenous use of amino acids has been more difficult to demonstrate than simple maintenance of nitrogen equilibrium. It is believed that such increases have been shown to occur in 3 patients in the present study (cases, 1, 2 and 4). The fact that these patients were observed for over considerable periods prior to the administration of amino acids without exhibiting increases in serum protein under very favorable circumstances of environment and diet makes it extremely unlikely that the increases in serum proteins observed after administration of amino acids were unrelated to this event. Since the reasons for the existence of the hypoproteinemia in the patients under discussion were, in all probability, different, the results obtained will be described in detail.

The increase in serum protein followed closely by increase in body weight (case 1) suggests that the amino acids not only contributed to the regeneration of serum protein but may have contributed to rebuilding of other protein tissues of the body. It is interesting also that the increase in total serum protein took place in the albumin fraction, just as is the case in periods of spontaneous improvement in instances of cirrhosis of the liver. Despite a return of the serum proteins to normal levels, anemia persisted. Since iron taken orally tended to cause diarrhea in this patient, large amounts of parenteral iron were given, the anemia responded slowly to this therapy, but, contrary to expectations, the new hemoglobin was formed without a fall in the serum proteins. Persistence of hypoproteinemia

13 (a) Elman, R. Parenteral Replacement of Protein with the Amino-Acids of Hydrolyzed Casein, *Ann Surg* **112** 594, 1940. (b) Shohl, Butler, Blackfan and MacLachlan.<sup>7</sup>

and anemia in spite of the fact that the patient's diet was considered adequate in all essentials necessary for regeneration of serum protein and production of hemoglobin may be explained by deficient absorption from a defective gastrointestinal tract. Whether or not a defect was present it is clear that the administration of easily utilizable intravenous acids helped this patient retain sufficient nitrogen for regeneration of serum protein, repletion of protein stores and production of hemoglobin.

That in case 2 the serum proteins prior to operation failed to increase was not unexpected, since it is well known that in the presence of infection the mechanism of serum protein regeneration may be impaired. When the source of infection was surgically eradicated, however, a small increase in serum proteins began to be apparent on the sixth day after operation and the level continued to rise slowly. This fact is of especial significance because the only source of nitrogen available during the postoperative period was supplied in the form of parenterally

TABLE 2—Data on a Group of Patients Treated with Amino Acids Intravenously

Patient	Age	Sex	Diagnosis	Complicating Factor	Response to Intravenous Amino Acids
H R	54	I	Hypertensive cardiovascular disease, right hemiplegia, parkinsonism, diabetes mellitus	Stone in common duct, with jaundice, diabetic acidosis	Appetite and diabetic control restored
I B	27	F	Rheumatoid arthritis of hips and spine	Bilateral arthroplasty of hip	Severe anorexia following each operation, corrected in each instance
M B	31	F	Postencephalitic parkinsonism	Hypocline toxicity	Anorexia uncontrolled by usual therapy, including intravenous injection of electrolytes; return of appetite five hours after use of amino acids
R L	22	F	Hodgkin's disease	Nausea, vomiting and anorexia following roentgen therapy	Prompt cessation of symptoms on two occasions
M L	68	M	Hypertrophy of prostate with diminution of renal function	Intestinal obstruction caused by carcinoma of sigmoid; resection of left portion of colon	Complete anorexia for no apparent reason ten days after operation; patient objected violently to gavage; anorexia overcome

administered amino acids. Rapid healing of the wound and an otherwise unusually smooth convalescence confirm previous observations concerning the importance of maintaining nitrogen balance and normal serum protein values in surgical patients.<sup>14</sup>

The increase in serum proteins following injections of amino acids in case 4 and the failure to increase in case 3 were discussed in a previous communication.<sup>10c</sup> The results are now reviewed after long periods of observation. At the time of the first report the 2 patients appeared to exhibit similar clinical and laboratory data, but it may be significant that in 1 (case 3) the condition has progressed into a rather typical chronic nephritis while similar changes have not taken place in the other (case 4), who appears at the time of writing to be in a fair state of health. In case 4, as in case 1, the increase in the albumin fraction was responsible for the rise in the level of serum protein. The ability of orally ingested amino acids to maintain the increase in the serum protein obtained by the intra-

14 (a) Whipple, A. O. The Critical Latent or Lag Period in the Healing of Wounds, *Ann Surg* **112** 481, 1940. (b) Mecray, P. M., Barden, R. P., and Ravdin, I. S. Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations, *Surgery* **1** 53, 1937. (c) Jones and Eaton.<sup>1a</sup>

venous use of amino acids has now been satisfactorily demonstrated over a period of nine months. The fact that the patient (case 4) failed to regenerate serum protein or hemoglobin on a diet that was considered adequate for these purposes until he was given amino acids intravenously raises an interesting problem. Whether his ability to absorb proteins as such from the gastrointestinal tract is impaired or whether he lacks certain of the enzyme systems necessary for the breakdown and subsequent utilization of proteins after they have been absorbed is not apparent from this study. That he was able subsequently to maintain the serum protein level with orally ingested amino acids suggests that his difficulty lies in handling of whole proteins and their split products. It is so unusual as to be worthy of note that twenty years' addiction to a narcotic (heroin [diacetyl morphine]) has been interrupted.

In a recent review on the plasma proteins, Madden and Whipple<sup>15</sup> discussed the role of the liver in the formation of these substances and the evidence presented points to that organ as being the site of production of albumin, fibrinogen and at least part of the globulins in the experimental animal. If the liver is the organ largely responsible for the formation of the plasma proteins in man as well, then the finding at autopsy of an atrophic liver in 1 of our patients (case 5) is a possible explanation for his inability to manufacture new serum proteins. In this connection the report of a dog with an Eck fistula that could form only about one tenth as much plasma protein on a standard diet as could control animals may be mentioned<sup>16</sup>. This animal consequently remained hypoproteinemic. At autopsy, the liver was found to be markedly atrophic.

The return of appetite following intravenous administration of amino acids (case 5) has been repeatedly demonstrated in our hospital in a variety of clinical states, but attempts were not made to study the utilization of the injected material. Table 2 briefly summarizes the data on a group of 5 patients, who were thus treated after the usual methods failed to relieve the apathy for food.

#### CONCLUSIONS

Amino acid solutions<sup>11</sup> intravenously administered in sufficient quantities have been shown in 1 instance to maintain positive nitrogen balance.

In certain patients injections of intravenous amino acids are followed by increases in serum proteins.

Solutions of amino acids given intravenously appear to be of value in relieving intractable anorexia.

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15 Madden, S. C., and Whipple, G. H. Plasma Proteins. Their Source, Production and Utilization, *Physiol. Rev.* **20** 194, 1940.

16 Knutti, R. E., Erickson, C. C., Madden, S. C., Rekers, P. E., and Whipple, G. H. Liver Function and Blood Plasma Protein Formation, *J. Exper. Med.* **65** 431, 1937.

# TRICUSPID STENOSIS

## INCIDENCE AND DIAGNOSIS

CURTIS F GARVIN, M D

CLEVELAND

Data concerning the incidence of tricuspid stenosis recently have been compiled by Cooke and White<sup>1</sup>. This indicates that the tradition of the rarity of tricuspid stenosis may be partly due to numerous compilations of isolated case reports and to discrepancies dependent on variations in defining stenosis. These investigators found that between 1920 and 1937 there were 217 cases of rheumatic heart disease noted in 4,300 autopsies at the Massachusetts General Hospital. In 47 of these the tricuspid valve was affected, and in 30 there was tricuspid stenosis thought to be of sufficient degree to be of clinical significance.

In these 30 cases of Cooke and White<sup>1</sup> the diagnosis was made before death in 1 and suspected in 2 more. Their conclusion was that the diagnosis of tricuspid disease is difficult, but that if due attention were paid to the history and the clinical examination of the patient and to the roentgenogram of the heart, the diagnosis would be made more frequently. No one sign in their experience was pathognomonic, but they listed in order of importance the following clues: a middiastolic murmur localized over the tricuspid area, chronic and well marked systolic pulsation of the deep jugular veins, ascites in the absence of congestion of the lungs, enlargement of the shadow of the heart to the right, deviation of the esophagus to the left, cyanosis and sometimes jaundice, enlargement of the liver with or without pulsation, persistently raised venous pressure and a prolonged circulation time for the right side of the heart.

This study of tricuspid stenosis is based on 13 cases proved to be such post mortem at the Cleveland City Hospital in the decade from January 1930 to December 1939, inclusive. During this period there were 6,548 autopsies, of which 119 pertained to patients who died primarily of rheumatic heart disease (there were many others that showed slight involvement of the heart by rheumatic fever). The 119 patients with fatal rheumatic heart disease included 43 (36.1 per cent) who had involvement of the tricuspid valve, in 13 of whom the process had advanced to definite tricuspid stenosis (10.9 per cent of the 119).

The valves affected in the whole group of 119 patients were

Mitral alone	28
Aortic alone	3
Mitral and aortic	45
Mitral and tricuspid	4
Mitral, aortic, and tricuspid	34
Mitral, tricuspid and pulmonic	1
Mitral, aortic, tricuspid, and pulmonic	4
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	119

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From the Department of Medicine of the Cleveland City Hospital and the Western Reserve University School of Medicine.

1 Cooke, W. T., and White, P. D. Tricuspid Stenosis, with Particular Reference to Diagnosis and Prognosis, *Brit Heart J* 3: 147 (July) 1941.

Thus, of 119 cases of death from rheumatic heart disease, the mitral valve was affected in 116 cases, the aortic in 86, the tricuspid in 43 and the pulmonic in 5

Study of the 13 cases of tricuspid stenosis failed to reveal any symptoms or signs valuable in diagnosis beyond those listed by Cooke and White. It was possible, however, to support especially a point brought out by Cooke and White in reference to pulsation in the neck veins. These investigators found that deep jugular pulsation signified tricuspid regurgitation only, whether due to functional or to organic disease. But they felt that there was a "*strong probability, in fact almost a certainty, of the presence of tricuspid stenosis in the case of a patient in the fourth or fifth decade with rheumatic heart disease who has had for years marked systolic deep jugular pulsation with little or no congestive failure*"

In the series studied here, of the 119 persons who died of rheumatic heart disease, 7 had significant chronic organic tricuspid insufficiency. Of these, at autopsy, 6 showed marked tricuspid stenosis, the seventh, slight stenosis. In short, *there was not a single case of organic tricuspid insufficiency without stenosis of some degree*. It would appear that the presence of tricuspid insufficiency considered clinically to be organic is strong evidence in favor of the diagnosis of tricuspid stenosis.

Of the 13 cases of tricuspid stenosis, 3 were diagnosed clinically. One of these is reported, chiefly because the stenosis was extraordinarily severe.

#### REPORT OF A CASE

J. D., a white man aged 36, who entered the Cleveland City Hospital Oct. 21, 1938, complained of shortness of breath. He had been in good health until May 1937, when he noticed weakness, shortness of breath on exertion, cough and swelling of his ankles. These symptoms became increasingly severe, so that he was virtually incapacitated during the year before he was admitted to the hospital. An acute psychosis with an attempt at suicide was the immediate cause for hospitalization. There was no past history of rheumatic fever.

Examination showed the patient to be well developed but orthopneic and acutely ill. The skin and the mucous membranes showed a combination of moderate cyanosis and slight icterus. The veins of the neck were distended with blood and pulsated. There were rales at the bases of the lungs. The liver was enlarged, the edge being 6 cm. below the costal margin, and definitely seemed to pulsate. The legs and the back were edematous.

The heart was much enlarged in all directions. There was a systolic thrill at the base, with a diastolic one at the apex. At the base and to the left of the upper part of the sternum there were a systolic and a diastolic murmur, the latter having the characteristics of one due to aortic insufficiency. At the apex there was a systolic murmur, as well as a diastolic murmur of a rumbling nature with a presystolic accentuation. In addition, a systolic and a diastolic murmur were noted in the xiphoid region. The cardiac mechanism was normal, and there was a gallop rhythm. The pulse was of the Corrigan type. The blood pressure was 184 systolic and 60 diastolic.

The venous pressure was 22 cm. of blood, and this increased to 28 cm. when the liver was pressed on. The decholin circulation (arm to tongue) time was forty-one seconds, and the ether circulation time was thirteen seconds. The vital capacity was 3,000 cc., which was 68 per cent of the estimated normal. Wassermann tests of the blood and the spinal fluid gave normal results. The specific gravity of the urine was 1.032, the reaction for albumin was grade 4. The red blood cell count was 6,000,000 per cubic millimeter, and the value for hemoglobin was 22.3 Gm. per hundred cubic centimeters of blood.

Fluoroscopic examination of the heart and roentgenograms of the chest showed the cardiac shadow to be considerably increased in size in all directions. The transverse diameter measured 23 cm. in relation to the greatest internal diameter of the chest, which was 35 cm. The left ventricle was greatly increased in size in both the posteroanterior and the second oblique view. In the first oblique view the left auricle was slightly enlarged and the pulmonary conus was prominent. The pulsations of the heart were increased in amplitude and were regular. The aorta was normal. The lung fields were clear.

The electrocardiogram showed left axis deviation, low voltage and splintering of the QRS complex in lead III.

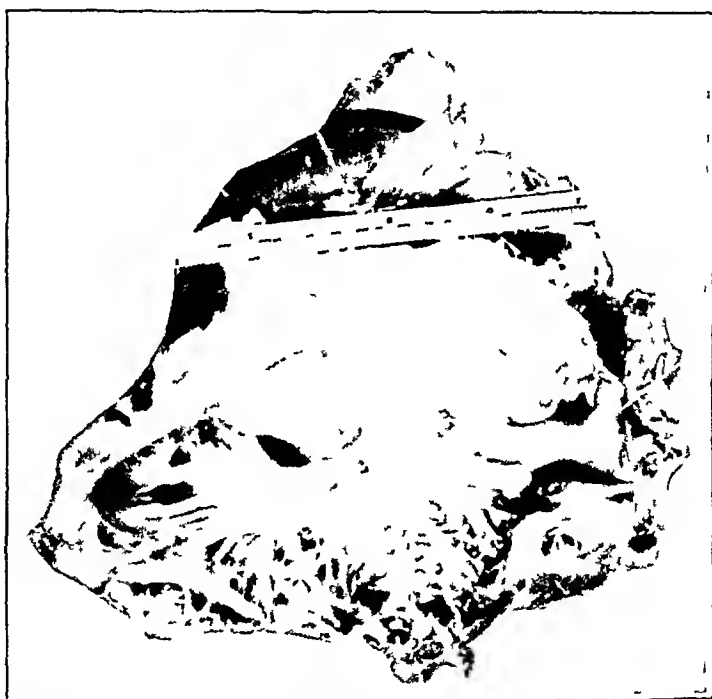
Despite appropriate treatment the patient's cardiac failure became increasingly severe. He died Jan 7, 1939.

The clinical diagnosis was rheumatic heart disease with aortic insufficiency and stenosis, mitral stenosis and insufficiency, tricuspid stenosis and insufficiency, cardiac hypertrophy and dilatation, and myocardial insufficiency.

*Autopsy* (Dr L L Terry)—External findings were negative except for pitting edema of the legs.

The heart weighed 825 Gm. The right atrium was slightly dilated, and the musculature was hypertrophied. The orifice of the tricuspid valve had a fish mouth appearance, the circumference measuring 3.5 cm (figure). The right ventricle was relatively small, and the wall measured 4 mm in thickness. The pulmonary valve was normal.

The left atrium was moderately dilated, the wall was thickened and the endocardium more opaque than usual. The mitral valve showed a moderate degree of stenosis, the circumference of the orifice being 6 cm. The left ventricle was markedly enlarged, and the wall measured 19 mm in thickness. The cusps of the aortic valve were adherent, and the edges were thickened and rolled in toward the sinuses of Valsalva. The coronary arteries were normal.



A markedly stenosed (fish mouth) tricuspid valve seen from above, in a case of chronic rheumatic heart disease.

The lungs showed severe chronic passive hyperemia with numerous recent and remote infarcts. The liver weighed 2,100 Gm and was the site of typical cardiac cirrhosis. The remaining viscera showed chronic passive hyperemia.

The diagnosis was chronic rheumatic heart disease with hypertrophy and dilatation, chronic rheumatic endocarditis with stenosis and insufficiency of the mitral, aortic and tricuspid valves, infarcts of the lungs, thrombi in the pulmonary arteries, cardiac cirrhosis of the liver, and chronic passive hyperemia of the viscera.

#### COMMENT

The clinical diagnosis of tricuspid insufficiency and stenosis in this case was made principally on the basis of the combination of a systolic and a diastolic murmur in the xiphoid region, the systolic jugular pulsation, the pulsation of the liver and the peculiar cyanotic-icteric appearance of the patient.

The degree of stenosis of the tricuspid valve was very severe. In none of the other cases studied was the stenosis as severe. It is notable that with an orifice so stenosed the jugular veins and the liver nevertheless showed pulsations. This indi-

cates that stenosis of even extreme degree need not prevent the phenomenon of insufficiency of the valve. The importance of the organic tricuspid insufficiency as an indication of probable stenosis has been noted.

Such marked tricuspid stenosis occurring in a male is also noteworthy. Smith and Levine<sup>2</sup> for example have pointed out the preponderance of females with tricuspid stenosis and have written that in their personal experience they have never encountered a male with marked tricuspid stenosis.

Smith and Levine also stated that in their cases the degree of stenosis of the mitral valve was always as great as or greater than that of the tricuspid valve. Again this case is exceptional, for the tricuspid stenosis was more severe than the mitral stenosis.

#### SUMMARY

Of 119 consecutive patients who died of rheumatic heart disease and were examined post mortem, 43 (36.1 per cent) showed involvement of the tricuspid valve, and in 13 of these the process had advanced to definite tricuspid stenosis (10.9 per cent of the 119 cases of rheumatic heart disease).

No new symptoms or signs helpful in diagnosis were discovered. The study did emphasize, however, the importance of chronic organic rheumatic tricuspid insufficiency as an indication that stenosis is likely, for in all the 7 cases of organic tricuspid insufficiency included in the series there was more or less stenosis.

Three cases of tricuspid stenosis were diagnosed clinically. One of the patients had very severe tricuspid stenosis, the circumference of the orifice measuring 3.5 cm. Nevertheless, clinically there was pulsation of the jugular veins and of the liver. Apparently marked stenosis of the tricuspid valve need not prevent the phenomena of tricuspid insufficiency.

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<sup>2</sup> Smith, J. A., and Levine, S. A. The Clinical Features of Tricuspid Stenosis, *Am Heart J* **23** 739 (June) 1942.



# CHOLESTEROL CONTENT OF THE URINE IN PATIENTS WITH CANCER

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WITH THE TECHNICAL ASSISTANCE OF

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In recent years, there has been an unusual amount of conjecture as to the significance of the configurational similarity of the sex hormones, bile acids, vitamin D, cholesterol and the carcinogenic polycyclic hydrocarbons. Much speculation has been devoted particularly to the chemical relationship between the sex hormones and carcinogenic principles in the etiology of cancer. Sobotka<sup>1</sup> quoted Cook, who stated that "the cell proliferation which characterizes the estrous state is in some respects reminiscent of the early stages of malignant growth," and Sobotka further conjectured that, while biodehydrogenation of sterols or bile acids may be the physiologic method for the production of the sex hormones, further dehydrogenation by a faulty mechanism may give rise to tumor-stimulating substances.

Sobotka and Bloch<sup>2</sup> were unable to find any positive chemical or biologic evidence for the presence of carcinogenic hydrocarbons in large quantities of pooled urine from patients with cancer. However, they were able to confirm their previously reported observation<sup>3</sup> that urine from such patients contained larger quantities of cholesterol than that of normal subjects. The hypercholesteremia was attributed either to an anomaly of cholesterol metabolism inherent in persons with cancer or to destruction of malignant tumor tissue, which is known to be rich in cholesterol. The latter theory was given preference. Cachexia as a possible cause for the increased excretion of urinary cholesterol was ruled out by control studies on cardiac and tuberculous patients. In 1940, Sobotka, Bloch and Rosenbloom<sup>4</sup> analyzed individual twenty-four hour specimens of urine from patients with cancer and compared the excretion of cholesterol with that of normal subjects and of patients afflicted with diseases other than cancer. Although hypercholesteremia was more frequent in patients with cancer, these authors said it was not pronounced enough to be called a consistent finding in association with malignant tumor. They explained the high values in some patients as possibly due to the inclusion of urine from patients with associated renal disease, who manifested hypercholesteremia because of the proteinuria.<sup>5</sup>

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From the Medical Research Laboratory, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University

1 Sobotka, H. The Chemistry of the Steroids, Baltimore, Williams & Wilkins Company, 1938, p. 98

2 Sobotka, H., and Bloch, E. Urine Extractives in Cancer, *Am J Cancer* **35** 50, 1939

3 Bloch, E., and Sobotka, H. Urinary Cholesterol in Cancer, *J Biol Chem* **124** 567, 1938

4 Sobotka, H., Bloch, E., and Rosenbloom, A. B. Urinary Cholesterol in Cancer II, *Am J Cancer* **38** 253, 1940

5 Brugger, M. Cholesteroluria in Bright's Disease, *Am J Clin Path* **5** 504, 1935

## METHOD AND MATERIAL

In the present investigation, twenty-four hour specimens of urine from 26 normal subjects, 28 patients with various diseases other than cancer and 32 patients with proved cancer were analyzed for cholesterol according to the procedure developed recently in this laboratory<sup>6</sup> A portion of each specimen was subjected simultaneously to a routine analysis for protein, sugar, etc On the day the urine was collected, venous blood was obtained for the determination of the plasma cholesterol content (modified Bloor procedure<sup>7</sup>) and of the sedimentation rate (Westergren<sup>8</sup>)

TABLE 1—*The Cholesterol Content of the Urine in 26 Normal Subjects (31 Determinations)*

Subject	Age	Sex	Results of Urinalysis	Urine		
				Volume Cc /24 Hr	Cholesterol *	
					Mg /100 Cc	Mg /24 Hr
1	30	M	Negative	1,030	0.07	0.76
2	23	M	Negative	1,240	0.02	0.27
3	26	M	Negative	600	0.12	0.72
4 A	22	F	Negative	740	0.21	1.52
B			Negative	1,110	0.12	1.31
5	45	F	Negative	623	0.16	1.01
6	36	F	Negative	1,010	0.17	1.74
7	19	F	Negative	675	0.13	0.90
8	19	F	Trace of protein	870	0.25	2.16
9	25	F	Negative	410	0.19	0.79
10	31	M	Negative	805	0.06	0.48
11 A	35	F	Negative	2,105	0.10	2.15
B			Negative	3,030	0.13	3.88
12	30	F	Negative	840	0.17	1.45
13	28	F	Negative	1,230	0.20	2.50
14	22	F	Negative	1,390	0.19	2.63
15	20	F	Faint trace of protein	730	0.20	1.46
16	27	M	Negative	1,390	0.18	2.53
17	28	M	Negative	1,510	0.15	2.23
18	28	F	Negative	630	0.32	2.21
19	25	F	Negative	605	0.41	2.49
20 A	25	F	Negative	1,430	0.19	2.72
B			Negative	1,510	0.22	3.25
C			Negative	1,180	0.15	1.76
D			Negative	775	0.22	1.72
21	27	M	Negative	600	0.09	0.56
22	40	M	Negative	640	0.15	1.00
23	21	F	Negative	920	0.18	1.67
24	20	F	Negative	900	0.26	2.36
25	19	F	Occasional red blood cell	730	0.16	1.16
26	25	F	Negative	960	0.12	1.16
Range					0.02-0.41	0.27-3.88
Mean					0.17	1.69
Standard deviation					±0.07	±0.85

\* The total output of cholesterol in twenty four hours was calculated by multiplying the actual volume of urine by the concentration of urinary cholesterol per hundred cubic centimeters to three places The volume of urine and the concentration of urinary cholesterol charted here and in tables 2 and 3 are given in round figures

## RESULTS

Table 1 shows the results for 26 normal subjects (interns, nurses, technicians and other hospital personnel) ranging in age from 19 to 45 years The excretion of cholesterol in the urine varied from 0.27 to 3.88 mg in twenty-four hours with a mean of  $1.69 \pm 0.85$  mg These values for normal subjects are appreciably higher

6 Bruger, M., and Ehrlich, S. B. On the Determination of Urinary Cholesterol, *J. Lab & Clin Med* **27** 1093, 1942

7 Sackett, G. E. Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum, *J. Biol. Chem.* **64** 203, 1925

8 Westergren, A. Die Senkungsreaktion, *Allgemein-klinische Ergebnisse, Praktische Bedeutung bei Tuberkulose*, *Ergebn. d. inn. Med. u. Kinderh.* **26** 577, 1924

than those previously reported" but the difference may be ascribed to the more accurate analytic procedure used in the present study

Table 2 indicates the results obtained for 28 patients with various disorders other than cancer. It will be observed that the mean excretion of cholesterol in this group was slightly higher than that of normal subjects (2.01 mg per twenty-four hours). For the most part, however, the individual variations fell well within the normal range. A cholesterol excretion of 4.24 mg in twenty-four hours being considered the upper limit of normal (mean plus three times the standard deviation), only patient 4, with cirrhosis of the liver, showed an abnormally high excretion of this

TABLE 2—*The Cholesterol Content of the Urine in 28 Patients with Various Clinical Disorders Other Than Cancer*

Patient	Age	Sex	Diagnosis	Results of Urinalysis	Sedimentation Rate Mm./Hr.	Plasma Cholesterol Mg./100 Cc.	Urine		
							Volume Cc./24 Hr.	Cholesterol Mg./100 Cc.	Mg./24 Hr.
1	65	M	Obstructive jaundice	7-10 WBC/HPT *	62	242	1,790	0.22	3.55
2	55	F	Pyelonephritis	Negative	73		975	0.14	1.74
3	57	F	Chronic diffuse glomerular nephritis	++ Protein	110	235	630	0.16	0.98
4	55	M	Cirrhosis of liver	Trace of protein	68		950	0.46	4.38
5	18	F	Cirrhosis of liver, juvenile	Negative	112	248	2,790	0.12	3.35
6	48	F	Cirrhosis of liver	Negative	45	137	400	0.32	1.26
7	55	M	Cirrhosis of liver	Negative	53	144	650	0.13	0.83
8	62	M	Lipoma	Negative	25	278	2,295	0.12	2.93
9	48	M	Fracture of skull	Negative	97	95	1,100	0.21	2.31
10	10	F	Acromegaly	Negative	20		1,210	0.27	3.28
11	76	M	Generalized arteriosclerosis	Negative			980	0.10	0.99
12	62	F	Generalized arteriosclerosis	5-10 WBC/HPT *	31	203	860	0.16	1.37
13	48	M	Generalized arteriosclerosis	Negative	23	230	1,150	0.05	0.62
14	67	M	Generalized arteriosclerosis	Negative		226	1,360	0.18	2.41
15	46	F	Generalized arteriosclerosis	Negative	25	206	630	0.34	2.11
16	59	F	Generalized arteriosclerosis	Negative	46	295	760	0.26	1.98
17	52	F	Rheumatic heart disease	Negative			420	0.58	2.42
18	15	F	Rheumatic heart disease	Negative	15	179	440	0.38	1.67
19	18	F	Rheumatic heart disease	Negative	10	102	630	0.25	1.6
20	24	F	Acute rheumatic fever	Many RBC	24	176	545	0.30	1.61
21	19	F	Acute tonsillitis	Negative	37	163	600	0.31	1.84
22	26	F	Chronic appendicitis	Negative	28	194	1,450	0.25	3.61
23	67	M	Herpes zoster	Negative		172	2,175	0.10	2.16
24	18	F	Exophthalmic goiter	Negative	40	205	325	0.33	1.07
25	61	M	Exophthalmic goiter	Negative	41	89	565	0.10	0.59
26	47	F	Exophthalmic goiter	Negative	39	180	545	0.20	1.09
27	48	F	Rheumatoid arthritis	Negative	45	144	420	0.56	2.36
28	54	F	Sciatic neuritis	Negative		205	900	0.25	2.21
Mean								0.25	2.01

\* White blood cells per high power field

sterol. His hypercholesteremia could be ascribed in part to the loss of protein in the urine. It will be observed further that there was little or no correlation between the sedimentation rate, the plasma cholesterol content and the degree of hypercholesteremia.

Table 3 details the clinical diagnosis, the diagnostic criteria, the results of routine urinalyses, the sedimentation rate and the plasma cholesterol content for 32 patients with proved cancer. The time relationship of the studies on urinary cholesterol to the duration of symptoms and to operation, death, etc., is also noted.

The occurrence of hypercholesteremia in patients with some types of cancer is shown. The excretion of cholesterol in the urine was abnormally high in 3 of 4 patients with carcinoma of the breast (patients 1, 2 and 4), in 3 of 9 with adenocarcinoma of the rectum (patients 8, 12 and 13) and in 2 of 5 with carcinoma of the

stomach or colon (patients 16 and 18) The excretion of excessive amounts of cholesterol in the urine was independent of proteinuria, since the urine of many of these patients failed to reveal detectable quantities of protein

In each of 6 patients with squamous or basal cell carcinoma of the skin, larynx or alveolar ridge, the excretion of cholesterol in the urine was not abnormal (patients 19 to 24) Normal values were also obtained for patients with carcinoma of the lung (patients 25 to 27), carcinoma of the bone (patient 28), primary carcinoma of the liver (patient 29), adenocarcinoma of the cervix (patient 30), papillary adenocarcinoma of the ovary (patient 31) and melanoma (patient 32)

It was observed that the highest urinary values for cholesterol were obtained for patients with adenocarcinoma of the rectum (patients 8, 12 and 13) This may have been a fortuitous observation because of the fewness of the patients studied, but such values as 27.9, 19.7 and 47.8 mg. in twenty-four hours are unusual Of interest was the observation that in 2 of the patients for whom serial determinations were carried out the urinary cholesterol decreased as the disease progressed (patients 12 and 13) No correlation was observed between the sedimentation rate, the plasma cholesterol content and the degree of cholesterinuria in these patients

#### COMMENT

Hypercholesterinuria is frequently encountered in patients with nephritis, particularly in those exhibiting a nephrotic component because of the associated loss of protein in the urine The increased excretion of urinary cholesterol in these patients may be explained by the chemotactic relationship existing between protein and cholesterol On the other hand, since cholesterol may exist in the blood as large molecular aggregates approximating the protein molecule in size both cholesterol and protein may filter through the pathologically permeable glomerulus<sup>10</sup> Whichever hypothesis is correct, in patients with Bright's disease the excretion of cholesterol in the urine parallels the loss of protein<sup>5</sup>

In some patients with cancer, however, large amounts of cholesterol may be excreted in the urine without any evidence of increased glomerular permeability (little or no proteinuria) It is rather difficult to explain this phenomenon unless one assumes that the cholesterol released into the blood stream by disintegrating malignant tumors is physicochemically different from the cholesterol normally present in the plasma Thus, if the sterols released by cancer tissue exist as single molecules or as micellae, diffusion through a normal glomerular membrane may be possible It may be stated here, however, that many experiments carried out in this laboratory have to date failed to reveal any abnormal physicochemical status of the plasma cholesterol in patients with cancer This phase of the problem is still being investigated

Though hypercholesterinuria is frequently encountered in patients with cancer, it is not an invariable finding This, too, is rather difficult to explain Obviously, much more investigation is required A prolonged study on a large number of patients may prove fruitful if planned to include such observations as a correlation of the cholesterinuria to the type, grade and duration of the cancer, to the presence or absence of metastases, to the effect of roentgen ray and radium therapy, to the results of surgical removal of the tumor and, finally, to the cholesterol content of the malignant tissue

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10 Bruger, M The State of Cholesterol and the Nature of the Cholesterol-Protein Complex in Pathological Body Fluids, *J Biol Chem* **108** 463, 1935

TABLE 3—The Cholesterol Content of the Urine in 32 Patients with Proved Cancer (36 Determinations)

Patient	Age	Sex	Diagnosis	Duration of Symptoms Months	Diagnosis Criteria	Results of Urinalysis	Sedimentation Rate Mm/Hr	Plasma Choles- terol Mg/100 Cc	Urine				Time Relationship *
									Volume Cc/24 Hr	Cholesterol			
										Mg/100 Cc	Mg/24 Hr		
1	71	F	Adenocarcinoma of left breast	1	Pathologic changes in tissue	15 WBC/HPF †	115		1,550	0.55	8.56		1½ months after radical left mastec- tomy
2	30	F	Adenocarcinoma of right breast	2	Pathologic changes in tissue	Negative	92	207	1,138	0.11	5.82		8 days after radical right mastectomy
3	40	F	Adenocarcinoma of left breast	6	Pathologic changes in tissue	Negative	95	276	565	0.39	2.18		7 weeks after radical left mastectomy
4	52	F	Sclerosing carcinoma of left breast	1	Pathologic changes in tissue	Negative	67	211	950	0.65	6.15		1 days after radical left mastectomy
5	43	M	Adenocarcinoma of rectum and sigmoid flexure	12	Pathologic changes in tissue	Negative	18		785	0.19	1.15		7 months after abdominal perineal resection
6	54	F	Adenocarcinoma of rectum	1½	Pathologic changes in tissue	Trace of sugar	38	2.6	3,110	0.08	2.61		Simultaneous with operation
7	37	M	Adenocarcinoma of rectum	12	Pathologic changes in tissue	Negative	110	271	900	0.23	2.07		Simultaneous with operation
8	50	F	Adenocarcinoma of rectum	12	Pathologic changes in tissue	Trace of protein, 0.5% sugar, many red blood cells	55	203	1,970	1.43	27.89		2½ months after colostomy
9	45	M	Adenocarcinoma of rectum	12	Pathologic changes in tissue	Negative			1,890	0.10	1.89		1½ years after abdominal perineal resection
10	48	F	Adenocarcinoma of rectum	5	Pathologic changes in tissue	Negative	223	2,570	0.09	2.40	7 months after abdominal perineal resection		
11A	75	M	Adenocarcinoma of rectum	72	Pathologic changes in tissue	Negative	148	850	0.25	2.10	2.10		3 years after colostomy
12A	62	M	Adenocarcinoma of rectum	7	Pathologic changes in tissue	Negative	18	1,270	0.14	1.74	Urinalysis 2 months later, death 2 months after this study		
B	50	F	Adenocarcinoma of rectum	12	Pathologic changes in tissue	Trace of protein, many red blood cells	47	4,125	0.15	10.71	11 days after colostomy		
13A	50	F	Abdominal carcinomatosis (metastatic)	12	Pathologic changes in tissue	Negative	113	1,840	0.20	3.66	Urinalysis 3½ months later		
B	51	F	Abdominal carcinomatosis (metastatic)	1	Pathologic changes in tissue	Negative	121	2,710	1.75	17.82	1 week after abdominal perineal resection		
C								2,700	0.77	20.63	Urinalysis 14 days later		
							38	1,850	0.62	9.64	Urinalysis 4 months later		
								540	0.34	1.83	Death 5 days later		

15	63	F	Carcinoma of stomach and lower end of esophagus	6	Macroscopic pathologic changes (operation)	Negative	11	233	177	0 77	1 30	Simultaneous with operation
16	39	M	Carcinoma of stomach with metastases to mesenteric lymph nodes	2	Pathologic changes in tissue	Negative	9	211	1,275	0 11	5 18	12½ days before an exploratory laparotomy, death 5 days later
17	61	F	Adenocarcinoma of transverse colon and sigmoid flexure	?	Pathologic changes in tissue	Negative	93	262	830	0 10	3 29	6 months after exploratory laparotomy
18	52	M	Adenocarcinoma of colon	3	Pathologic changes in tissue	Trace of sugar, numerous white blood cells	29	172	1,800	0 16	8 35	1½ months after ileocelectomy
19	57	M	Squamous cell carcinoma of cheek	12	Pathologic changes in tissue	Negative	17	218	600	0 23	1 65	1 week after dissection and plastic repair
20	56	M	Squamous cell carcinoma of larynx	2	Pathologic changes in tissue	Negative	26	1,100	1,100	0 21	2 66	2 days after tracheotomy and direct laryngoscopy with biopsy
21	59	M	Squamous cell carcinoma of upper alveolar ridge	12	Pathologic changes in tissue	Negative	106	199	110	0 22	0 88	3 days after electrocoagulation and endothermic excision
22	57	M	Basal cell carcinoma of skin	108	Pathologic changes in tissue	67 WBC/HPF	19	230	1,550	0 13	2 02	1 month after excision and plastic repair
23	51	M	Basal cell carcinoma of skin	18	Pathologic changes in tissue	Negative	40	217	2,110	0 11	2 89	2 days after excision and plastic repair
24	70	M	Squamous cell carcinoma of mouth	12	Pathologic changes in tissue	Negative	85	165	1,150	0 15	2 18	
25	50	F	Carcinoma of lung (secondary)	6	Röntgenologic changes	Negative	10	191	310	0 86	2 91	1½ years after radical left mastectomy
26	59	F	Carcinoma of lung (secondary)	12	Röntgenologic changes	Negative	10	171	1,150	0 19	2 72	12 years after radical left mastectomy
27	57	F	Carcinoma of lung (primary)	21	Röntgenologic changes	10 20 WBC/HPF	98	172	920	0 32	2 96	
28	39	M	Carcinoma of right humerus and second lumbar vertebra (metastatic)	1	Röntgenologic changes	Negative	30	193	830	0 11	1 19	
29	47	F	Carcinoma of liver (primary)	9	Pathologic changes in tissue	Negative	95	232	880	0 23	2 06	2 weeks after punch biopsy, death 1 weeks later
30	21	F	Adenocarcinoma of cervix	?	Pathologic changes in tissue	Negative	39	218	590	0 66	3 01	1½ days after uterine curettage
31	66	F	Papillary adenocarcinoma of right ovary with metastases to abdominal viscera	2	Pathologic changes in tissue	+ Protein, 5-10 WBC/HPF	18	109	350	0 20	0 76	Death 1 day later
32	43	M	Melanosarcoma (metastatic)	1	Pathologic changes in tissue	Negative	109		1,860	0 22	4 15	2 weeks after resection of bilateral inguinal node
Mean										—	—	6 09

\* Time relationship between determination of urinary cholesterol and operation, death, etc

† White blood cells per high power field

## SUMMARY AND CONCLUSIONS

The excretion of cholesterol in the urine in 26 normal subjects ranged from 0.27 to 3.88 mg in twenty-four hours with a mean of  $1.69 \pm 0.85$  mg. In 28 patients with a variety of clinical disorders other than cancer the mean excretion of cholesterol was slightly higher than in normal subjects (2.01 mg in twenty-four hours) but for the most part the individual variations fell well within the normal range. In 8 of 32 patients with cancer, the excretion of cholesterol in the urine was significantly elevated above normal, the highest value noted was 47.8 mg in twenty-four hours in a patient with adenocarcinoma of the rectum. The mean amount of urinary cholesterol for this group was 6.09 mg in twenty-four hours. No correlation was observed between the sedimentation rate, the plasma cholesterol content and the degree of cholesterinuria. Hypercholesterinuria occurs independently of loss of protein in the urine, some theoretic considerations are offered to account for this phenomenon.

301 East Twentieth Street

# Progress in Internal Medicine

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## BLOOD

A REVIEW OF THE RECENT LITERATURE

FRANK H BETHELL, M D

CYRUS C STURGIS, M D

ROBERT A HETTIG, M D

AND

OTTO TOD MALLERY JR, M D

ANN ARBOR, MICH

*(Continued from Page 903)*

### APLASTIC ANEMIA AND REFRACTORY ANEMIAS

No new and important information concerning aplastic anemia was reported in 1942, with the possible exception that the condition may follow the use of sulfathiazole. A paper by Vaughan<sup>180</sup> deals with 34 cases of aplastic anemia, both of the primary and of the secondary type. He quotes Rosenthal as stating that the disease may be defined as a progressive condition of unknown cause characterized by severe anemia, leukopenia, thrombopenia, and marrow acellularity. When it does not conform to this description it is regarded as atypical. The cases in which a cause for the disease can be ascertained are segregated as cases of the secondary type. Vaughan considers aplastic anemia in the broader sense, which includes the two subgroups indicated. Ten of the cases were of the secondary type, in 6 of these the anemia was due to anisphenamine and in 4 to benzene. The remaining cases were regarded as instances of the cryptogenic variety of aplastic anemia, although in 2 there was toxemia of pregnancy and in 1 military tuberculosis. The author emphasizes that accurate classification is highly desirable but by no means simple, as adequate means for making a differentiation are not always available. Moreover, the history of exposure is not always easy to interpret. The symptoms and signs in this group were those usually observed, with the following exceptions. In 34 per cent of the patients there was some degree of enlargement of the lymph nodes clinically, 15 per cent had enlargement of both the lymph nodes and the spleen, and 12 per cent had enlargement of the lymph nodes, the spleen and the liver. These clinical observations were substantiated by necropsies. In a great majority of the cases the classic findings of severe anemia, leukopenia and thrombopenia were present. In 27 per cent the anemia was macrocytic, in 54 per cent normocytic and in 19 per cent microcytic. In only a single instance was achlorhydria present, and that was a case of macrocytic anemia. Usually there was a reduction in the number of mature polymorphonuclear cells, with relative lymphocytosis. Bone marrow was obtained in 26 of the 34 cases—either during life, by sternal puncture or by trephination, or at necropsy, by the usual technic. In some instances both ante-mortem and postmortem observations were made. In 12 of the cases the marrow showed a remarkable reduction of cellularity, in 8 there was much greater cellu-

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180 Vaughan, S. L. Aplastic Anemia, New York State J. Med. **42** 978, 1942



larity, with variation in appearance in the sections obtained from different areas, in 2 there seemed to be distinct hyperplasia, and in 1 hypoplasia, which did not reach the degree of acellularity previously described

The general findings in the 14 cases which came to necropsy were as follows in 5 cases, splenomegaly, which was an outstanding feature in 2 cases, in 4, hepatomegaly, in 7, bronchopneumonia, and in 2, pleuritis. In 10 cases diffuse hemorrhagic phenomena were present, and in 3 these phenomena seemed to be the most pronounced of the terminal features. In 3 cases ulcerative lesions with or without sepsis were present, and in 1 case this was the most conspicuous feature.

The outcome of the disease in the 34 cases was as follows: complete recovery in 15 per cent, death in 73 per cent, result pending in 12 per cent. The results indicate the extremely high mortality of the series as a whole, and a somewhat better outlook in cases of the secondary as opposed to cases of the cryptogenic type.

The following eleven agents were employed in treatment: blood by transfusion and by intramuscular injection, iron, liver products, vitamins, yellow bone marrow, pentnucleotide (the sodium salts of pentose nucleotides from the ribonucleic acid of yeast), roentgen rays, ultraviolet rays, endoglobulin, sulfonamide compounds, and marrow by transfusion, in addition, splenectomy and uterine curettment were performed. Of the measures mentioned, only blood transfusions were used in all the cases. The author concludes that in some cases they have been instrumental in prolonging life until a remission could occur. The study led the author to conclude that aplastic anemia should be regarded as a disorder of varied manifestations in which the fundamental defect is one of general hemopoietic insufficiency varying from inhibition of normal maturation and distribution of cells to actual hyperplastic changes.

Meyer and Perlmutter<sup>181</sup> emphasize that the untoward hematologic changes following the use of the sulfonamide compounds fall into two main groups, namely, agranulocytosis and hemolytic anemia, but that leukemoid reactions and thrombopenic purpura have also been observed. According to the authors, their case is the first one of aplastic anemia due to the use of such drugs to be reported. The patient was a 55 year old Assyrian woman in whom bronchopneumonia developed and who was given 12 Gm of sulfathiazole over a period of two days. At the end of that time, on admission to the hospital the blood findings were as follows: hemoglobin, 5 Gm, red blood cell count, 1,710,000 per cubic millimeter, white blood count 1,000, with polymorphonuclears 8 per cent, lymphocytes 88 per cent, monocytes 4 per cent and platelets none. Sternal marrow obtained by aspiration showed hypoplasia with suppression of the cellular components. With cessation of the administration of sulfathiazole and with blood transfusions and injections of liver extract and pentnucleotide there was a rapid rise in the blood platelet count, the hemoglobin level and the number of red and white blood cells. At the time of death, twenty-two days after admission, the hemoglobin value was 7.0 Gm, the red blood cell count 1,600,000 and the white blood cell count 20,500, with 38 per cent polymorphonuclear cells, only rare platelets were present. A second sternal puncture, made six days after the initial one, is stated to have yielded an "essentially normal differential smear." Postmortem sections of the marrow showed moderate hyperplasia, with all of the usual cellular elements present. The authors emphasize that the aplastic picture was evident after the administration of only 12 Gm of the sulfonamide compound over a period of two

181 Meyer, L. M., and Perlmutter, M. Aplastic Anemia Due to Sulfathiazole, *J. A. M. A.* 119:558 (June 13) 1942.

days and that the case shows that the marrow may return to normal with discontinuance of the administration of the drug. No mention is made of previous medication with sulfonamide compounds which might have sensitized the patient to subsequent doses. In the absence of sensitization it is remarkable that such a serious dyscrasia of the blood should develop following such a small total dose. Furthermore, it is not established with certainty that the aplastic anemia in this patient was actually a result of the medication, as such a condition due to an unknown cause may have been present independently and concurrently.

An unusual case of aplastic anemia, in which the organs at necropsy showed the changes of hemochromatosis, is presented by Mackey<sup>182</sup>. The patient, a laborer aged 46 years, had the disease for three and one-half years, during which time he received thirty-nine blood transfusions. At one time, for a short interval, he felt so well that he presented himself to the hospital as a donor. At this time the red blood cell count and the hemoglobin content were within normal limits. The period of remission, however, was brief, as a blood transfusion was required a short time later. It was suggested that the changes characteristic of hemochromatosis may have been due to storage of iron in the various tissues, as the body was unable to utilize it in the formation of hemoglobin.

Hurwitt and Field<sup>100</sup> observed the case of a 27 year old woman who died in the fourteenth week of pregnancy of severe anemia which had all the characteristics of the so-called idiopathic aplastic type. In a group of 14 cases of aplastic anemia occurring during pregnancy, which were collected from the literature, there were only 5 in which the patient survived. In all of these, the uterus had been emptied, by normal delivery in 2 and by interruption during the third trimester in 2. In 1 case the disease developed post partum. They believe that the association of this variety of anemia with pregnancy is more than coincidental, in other words, that the gravidity may play an etiologic or a conditioning role. They advise that in the presence of this variety of anemia interruption of the pregnancy be strongly considered.

Sterne<sup>183</sup> reports the case of a 39 year old white man who had a red blood cell count of 1,500,000 per cubic millimeter, a hemoglobin value of 5.3 Gm., a white blood cell count of 1,350, with 30 per cent neutrophils, and a platelet count of 12,200. The differential diagnosis rested between subleukemic leukemia and panhypoplasia of the marrow due to treatment with neoarsphenamine. The absence of pathologic leukocytes in the circulating blood ruled out the former, and aspirated marrow showed the characteristic picture of the latter. Of the four methods of therapy, transfusion of blood, injection of pentnucleotide, administration of yellow bone marrow and intrasternal infusion of the marrow, the first mentioned is regarded as the most satisfactory by the author.

The case of an Italian aged 50 years in whom severe aplastic anemia developed during the course of six injections of neoarsphenamine is reported by Sayer<sup>184</sup>. Examination of his blood showed the hemoglobin content 35 per cent of normal and the red blood cells 1,500,000, the white blood cells 2,200 and the platelets 40,000 per cubic millimeter. Recovery followed injections of pentnucleotide and repeated blood transfusions.

182 Mackey, R. An Unusual Case of Aplastic Anemia with Organ Changes Resembling Haemochromatosis, *M. J. Australia* **1** 172, 1942.

183 Sterne, E. H., Jr. Leukopenia and Anemia After Therapy. Differential Diagnosis, *Cincinnati J. Med.* **23** 173, 1942.

184 Sayer, A. Aplastic Anemia Due to Arsphenamine, Stomatitis of Unknown Origin, *Arch. Dermat. & Syph.* **46** 453 (Sept.) 1942.

A case of aplastic anemia is reported by Meyer and Ginsberg<sup>185</sup> in which there was a period of ten years between the exposure to benzene and the development of symptoms. The history and physical findings were typical of this type of anemia and the case terminated fatally fourteen days after the patient's admission to the hospital. The diagnosis was verified by necropsy. There does not seem to be any doubt that the patient was extensively exposed to benzene ten years before the development of symptoms, and it is likewise clear that he succumbed to the condition which we call aplastic anemia. But there is no evidence to indicate that the benzene played a role in the causation of the disease inasmuch as the same condition may develop without a recognizable cause.

Beizer and Watkins<sup>186</sup> report their findings from examination of sternal marrow obtained by aspiration in 12 cases of refractory anemia in which the clinical picture was that of aplastic anemia. Cases in which there was evidence of depression of the activity of the marrow and of relative lymphocytosis followed the usual clinical course with death occurring in a relatively short time. On the other hand cases with evidence of hyperplasia of the marrow but with no observable lymphocytosis did not terminate fatally.

#### GRANULOCYTOPENIA AND AGRANULOCYTOSIS

The literature in 1942 includes reports of cases of agranulocytosis following the administration of sulfanilamide, sulfapyridine and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). When the widespread use of these drugs is considered the incidence of this grave complication does not seem great. It is now thought that the persons in whom agranulocytosis develops are sensitized to the drugs or become sensitized to them during the course of therapy. Controversy continues concerning the treatment of this disorder. It is of interest to note that opinion seems to favor the employment of sulfonamide drugs as therapeutic agents if the syndrome of agranulocytosis has not been induced by them.

Metzger,<sup>187</sup> in a memorial to Philip King Brown, records the little known fact that the latter was the first to describe the syndrome of agranulocytosis in an article published in 1902 in *American Medicine*, volume 3, page 649, entitled "A Fatal Case of Acute Primary Infectious Pharyngitis with Extreme Leukopenia." Thus twenty years before Werner Schultz published his classic paper dealing with the disease Brown had described this condition accurately and completely, as any one can determine by consulting his original paper.

Henry Jackson, Jr. in a review<sup>188</sup> of the current literature dealing with agranulocytosis, expresses himself rather positively on several controversial points. He agrees that in the great majority of cases this disease is secondary to the action of some drug but is inclined to believe that there are a few instances in which it is truly idiopathic. Such cases, in the opinion of the author, are exceedingly rare and are becoming more so as knowledge of the malady increases. He also believes that severe neutropenia indistinguishable from classic agranulocytosis may be secondary to overwhelming sepsis. According to him, it is difficult, if not impossible, to distinguish between idiopathic agranulocytosis and the leukopenia that is

185 Meyer, L. M., and Ginsberg, V. Aplastic Anemia, *J. Indust. Hyg. & Toxicol.* **24** 37, 1942.

186 Beizer, L. H., and Watkins, C. H. Sternal Marrow in Aplastic Anemia, *J. Clin. Investigation* **21** 636, 1942.

187 Metzger, J. Philip King Brown, M. D., *Tr. Am. Clin. & Climatol. A.* (1941) **57** 44, 1942.

188 Jackson, H., Jr. Medical Progress. Leukopenia, Agranulocytosis, *New England J. Med.* **225** 978, 1941.

due to the action of certain drugs, overwhelming sepsis or industrial poisoning (In our opinion, true agranulocytic angina may sometimes be differentiated from the neutropenia of sepsis, because the latter rarely is associated with complete absence of neutrophils from the blood stream, which rarely make up less than 10 per cent of the leukocytes. Complete absence of neutrophils commonly occurs in true agranulocytosis.) It is emphasized that at present aminopyrine is less commonly provocative of the malady, because its dangers are now widely recognized and in some countries its sale is limited by law. Gold preparations may occasionally cause the condition, and there is an ever increasing number of cases of grave granulocytopenia due to the sulfonamide compounds. In the author's opinion it is probable that any of these preparations may be responsible for the disease. In a series of 109 collected cases he found the causative agents to be as follows: sulfanilamide in 34, sulfapyridine in 8, aminopyrine alone in 39, allonal (allylisopropylbarbituric acid with aminopyrine [before 1939] or acetophenetidin [since 1939]) in 7 and causalin (aminodimethylpyrazolon quinoline sulfonate) in 4. In decreasing frequency, the following drugs were considered to be causative: cibalgine (aminopyrine and a barbitol derivative [dial]), acetanilid, amidophen (aminopyrine, acetophenetidin, caffeine and extract of hyoscyamus), cinchophen, amytal compound (amytal and aminopyrine), bismarsen and neocinchophen. Jackson acknowledges that the treatment of the disorder still remains a matter of debate. He makes a number of excellent points, however, with which we are in entire agreement concerning the administration or the continuation of the use of sulfonamide compounds in the presence of extreme leukopenia, thus, if the latter condition is obviously due to the drug, it should be stopped immediately, but if it is secondary to an infection which ordinarily is amenable to treatment with the sulfonamide compounds, these therapeutic agents should at once be given along with pentnucleotide, in an attempt to restore the leukocyte count to normal. Jackson contends rather strongly that the mere withdrawal of the offending drug does not always suffice to restore the white blood cell picture to normal, and hence other measures, such as the administration of pentnucleotide, should be employed. In support of this view Jackson cites his observations on 72 personally collected cases of agranulocytosis due to sulfonamide compounds or other drugs, in 30 per cent of which recovery followed the withdrawal of the drug without other specific medication. Of 26 similar cases in which the drug was withdrawn and adequate amounts of pentnucleotide were given (40 cc daily), recovery occurred in 66 per cent. Jackson gives a timely warning that all patients who are under treatment with drugs known to cause the condition should have frequent leukocyte and differential counts. If the total granulocyte count is found to be low, administration of the drug should be stopped and intensive treatment instituted at once, whether one chooses to treat by injections of pentnucleotide, frequent blood transfusions, administration of yellow bone marrow or a combination of these measures. He states as previously, that if pentnucleotide is given, not less than 40 cc should be administered daily, and its use should be continued until a favorable response has occurred or until it is apparent that no benefit will occur.

With a sweeping and to us unjustified statement, Dameshek and Wolfson<sup>189</sup> cast aside as worthless practically all forms of therapy which have been introduced in connection with agranulocytosis. Included in this relegation are the pentose nucleotides, adenine sulfate, liver extract, transfused blood and yellow bone marrow.

189 Dameshek, W., and Wolfson, L. E. A Preliminary Report on the Treatment of Agranulocytosis with Sulfathiazole, *Am J M Sc* **203** 819, 1942.

extract In our opinion their statement is unsupported, to say the least, and is not in accord with the experience of a majority of those who have had to deal with this disease On the other hand, the authors make a point well worth while when they emphasize that death probably results from overwhelming sepsis in a body stripped of its defensive granulocytes They treated 2 patients for severe agranulocytosis with blood transfusion and administration of pentose nucleotides, liver extract and sulfathiazole in large doses The recovery in each case is attributed in part at least to the effect of the sulfonamide compound on the sepsis Physicians are reluctant to give these drugs in the presence of leukopenia because occasionally agranulocytosis may develop in association with such therapy Long and Bliss reported in 1939 that when leukopenia is due to an infectious process no harm will result from the use of a sulfonamide compound and that with this therapy the infection may be overcome, with subsequent increase in the leukocyte count and recovery of the patient After careful consideration of the problem we concur in this opinion, for it does not follow that when leukopenia results from one cause, such as the effects of a drug, a patient will be sensitive in the same manner to another substance with which that drug has not even a remote chemical relationship Furthermore, as the authors have emphasized, sepsis associated with agranulocytosis is one of the major problems and is the condition which ordinarily leads to the fatal issue As the sulfonamide compounds are now the agents most effective against infection, particularly of the sort observed in association with agranulocytosis, their possible beneficial effect should not be denied to the patient

Barsby and Close<sup>190</sup> state that Beck in 1933 classified agranulocytosis as of five types fulminating, subacute, subchronic, recurrent and cyclic They state, however, that the classification is unsatisfactory because some patients show the characteristic symptoms of more than one type They report the case of a woman of 41 years who had pyrexial attacks with sore throat, ulcers of the mouth, a pink rash, pains in the joints, cough, abdominal pain and vomiting These episodes had occurred three to seven days after her menstrual periods over an interval of four years For the last seven months at least of the patient's illness these attacks were associated with neutrophil agranulocytosis Only twice during the period of observation was the number of polymorphonuclear cells greater than 3,000 per cubic millimeter, on five occasions they disappeared entirely for four or five days Necropsy disclosed pericecal inflammation and pulmonary abscess, no cause for the blood changes could be found The fact that the condition was recurrent and seemed related to the menstrual periods would lead us to suspect strongly that the patient had been taking some drug, such as aminopyrine In fact, after the patient's death it was discovered that she had been taking "Yeast-Vite," but this was considered as not a likely cause of the condition because the attacks were intermittent and because, according to the authors, this preparation has not contained aminopyrine since 1935 Neither objection, however, includes with certainty aminopyrine or a related compound as the significant etiologic factor

Schackle<sup>191</sup> refers to the case described by Barsby and Close and records from memory a similar illness in a child aged 5 whom he observed sixteen years ago This child experienced attacks of pyrexia at monthly intervals, each accompanied by more or less complete absence of polymorphonuclear cells from the circulation It was possible to predict the acute febrile rise by the preceding

190 Barsby, B E, and Close, H G Recurrent Neutrophil Agranulocytosis, *Lancet* 1 99, 1942

191 Shackle J W Recurrent Neutrophilic Agranulocytosis, *Lancet* 1 306 1942

reduction of these cells in the blood. Blood transfusions seemed to be of benefit, but the condition finally terminated fatally. Permission for necropsy was not obtained.

Waugh<sup>192</sup> gives a review of the changes which may occur in the blood following the introduction into the body of certain chemicals and drugs. He states that various substances may affect all of the hemopoietic activities of the marrow, producing a disorder which he calls "panmyelotoxicosis." Among these are arsenic, asphenamine, bismuth, aminopyrine and other benzene ring derivatives. Moreover, similar paralytic effects may be produced by various forms of radiation, such as the roentgen ray, radium and thorium, either after therapy or when poisoning has occurred. He emphasizes that sulfanilamide may produce granulocytopenia, and that this may result from a small amount of the drug, as indicated in 1 case in which death occurred following the administration of only 8 Gm. In general, however, it is his belief that although the quantity given seems to make a difference, individual susceptibility is probably even more important. Two deaths following the use of sulfonamide compounds were noted in the department of pathology of McGill University. He reports that the marrow almost always reveals a characteristic deficiency in maturing myelocytes and that the immature root cells and syncytial reticuloendothelial elements are unusually conspicuous. He expresses the view that future investigations may disclose that the action of these drugs is not toxic paralysis but deficiency paralysis due to removal of some important substance necessary for the maturation of the proliferating elements of the marrow. In the treatment of agranulocytosis he recommends transfusions of blood, administration of pentose nucleotides and recognition and withdrawal of the causative agent.

Three cases of granulocytopenia, 1 in which it was due to sulfanilamide and 2 in which it was due to sulfathiazole, are reported by Carley and Reid<sup>193</sup>. One of the patients who received sulfathiazole succumbed.

Fatal agranulocytosis following the use of sulfathiazole in a man aged 58 years is reported by Thompson<sup>194</sup>. The patient had been ill at home for two weeks with an infection of the respiratory tract and was treated for this with an unknown amount of the drug. After his admission to the hospital, the administration of the drug was resumed at the rate of 45 grains (2.91 Gm.) daily until he had received a total dose of 235 grains (15.23 Gm.). In addition, over this same period approximately 160 grains (10.36 Gm.) of acetylsalicylic acid was given. The minimum white blood cell count was 100 per cubic millimeter, all of which were lymphocytes. The sternal marrow was interpreted as typical of aplastic anemia. Data regarding the hemoglobin content of the circulating blood and the red blood cell count are not given. The author expresses the opinion that the incidence of agranulocytosis is very low in proportion to the number of patients receiving sulfathiazole but that it is a complication which should be kept in mind nevertheless and one which should be guarded against by repeated blood counts.

Cross<sup>195</sup> presents the case of a man aged 20 in whom agranulocytosis developed, with a minimum leukocyte count of 1,000 per cubic millimeter and no polymorphonuclear leukocytes, following the administration of 42 Gm. of sulfapyridine over a

192 Waugh, T. R. Hematologic Aspects of Chemotherapy, Arch. Otolaryng. **35** 990 (June) 1942.

193 Carley, P. S., and Reid, P. E. Granulocytopenia Resulting from Sulfonamide (Sulfanilamide and Its Derivative, Sulfathiazole) Therapy. Case Reports and Discussion, Urol. & Cutan. Rev. **46** 19, 1942.

194 Thompson, L. Agranulocytosis Due to Sulfathiazole, Northwest Med. **41** 133, 1942.

195 Cross, R. M. Recovery from Agranulocytosis After a Rigor During Transfusion, Lancet **1** 9, 1942.

period of ten days. Treatment was by injections of pentnucleotide and repeated blood transfusions. During the course of the last transfusion the patient, for no known reason experienced a severe rigor lasting for about fifteen minutes. Blood films taken immediately thereafter showed a slight increase in the total number of leukocytes and in the percentage of neutrophils. Four hours later, however, there was an increase to 40,000 per cubic millimeter, 85 per cent of which were neutrophils most of them immature. The patient's temperature rose to 105.6 F shortly after the chill but the next morning it became and remained normal. Complete recovery followed. The suggestion is made that as the rigor and fever seemed to terminate the course of the agranulocytosis abruptly, induced and controlled hyperpyrexia, such as that caused by protein shock, might be useful in aborting attacks of this disease.

A fatal case of agranulocytosis following the administration of sulfapyridine for nonvenereal urethritis is reported by Conti.<sup>196</sup> The author warns that although the majority of reactions following the use of the sulfonamide compounds are nonfatal and transient, each patient receiving such therapy should be under close supervision, as severe reactions such as agranulocytosis and hemolytic anemia, do occur. The patient whose case was the subject of report received a total of 405 grams (26.24 Gm.) of sulfapyridine over a period of six days. After a latent period of two weeks, fever and chills appeared, and the red blood cell count was found to be 3,280,000 per cubic millimeter, the white blood cell count was 1,900 per cubic millimeter, with 98 per cent lymphocytes, 2 per cent monocytes and no neutrophils. The patient died on the fourth day of observation at which time the white blood cell count was 11,600, with 25 per cent blast cells, 5 per cent promyelocytes and 20 per cent myelocytes. No necropsy was performed, nor was a sternal puncture done. The unusual blood picture just before death, as well as the unexplained latent period of two weeks, raises in our opinion the possibility that the patient may have succumbed to an acute form of leukemia rather than to agranulocytosis.

John<sup>197</sup> presents the case of a man aged 23 who had severe agranulocytosis following two courses of sulfapyridine therapy for an abscess of the lung. Some confusion arises, however, concerning the cause in this case, for with each course of sulfapyridine therapy the patient was also given allonal. No statement is made whether the latter preparation was the older type which contained amipyrine (before 1939) or the more recent combination in which this drug has been replaced by acetophenetidin (since 1939).

Levin and Bethell<sup>198</sup> report the first case in the literature of agranulocytosis that was undoubtedly due to sulfadiazine. Leukopenia following the use of this drug had been previously noted. The authors emphasize that other sulfonamide compounds are known to be responsible for agranulocytosis that although granulocytopenia usually develops after prolonged use of the drug, it may occur after administration of a small dose, and that the concentration of the sulfanilamide derivative in the blood gives no indication of the likelihood of ensuing granulocytopenia. It is their opinion that patients in whom this condition develops must be assumed to have had a preexisting idiosyncrasy for the drug or to have acquired such an idiosyncrasy during the course of its administration. The case reported

196 Conti, M. E. Malignant Granulocytopenia Following Sulfapyridine Therapy. Case, U. S. Nav. M. Bull. **40** 165, 1942.

197 John, J. B. Agranulocytosis Following Sulfapyridine (Sulfanilamide Derivative) and Allonal Therapy. Case, Laval med. **7** 191, 1942.

198 Levin, M., and Bethell, F. H. Fatal Granulocytopenia Developing During Administration of Sulfadiazine (Sulfanilamide Derivative), Univ. Hosp. Bull., Ann Arbor **8** 30, 1942.



by the authors was that of a man of 70 years who had undergone resection of a gangrenous ileum in a strangulated right inguinal hernia twenty-seven days prior to his death. He received a total of 76 Gm of sulfadiazine during a period of nineteen days. On the eighteenth day, the red blood cell count was 4,400,000 per cubic millimeter, the hemoglobin content was 11.5 Gm per hundred cubic centimeters, the blood platelet count was 140,800 per cubic millimeter and the white blood cell count was 850 per cubic millimeter, with 2 per cent polymorphonuclears. The sternal marrow showed myeloblasts and early myelocytes, with little evidence of maturation beyond the myelocyte stage.

Curry<sup>199</sup> reports the case of a 41 year old woman in whom acute agranulocytosis developed, with a minimum white blood cell count of 650 per cubic millimeter and complete absence of polymorphonuclear leukocytes, following the administration of sulfadiazine. The patient had a diagnosis of portal cirrhosis with acute hepatitis and was given the drug on the ninth day in the hospital because of fever and roentgen evidence of bronchopneumonia. In all, the patient received 140 Gm over a period of twenty-three days at the approximate rate of 6 Gm a day. At the time of the development of the agranulocytosis the concentration of sulfadiazine in the blood had reached 28.3 mg per hundred cubic centimeters. Recovery followed discontinuance of the drug, administration of pentnucleotide and transfusions of blood.

In a discussion<sup>200</sup> before the Section of Laryngology of the Royal Society of Medicine on involvements of the throat and nose in diseases of the blood, agranulocytosis is mentioned along with hemophilia, Osler's disease (hemorrhagic telangiectasia), leukemia, achlorhydric anemia, avitaminosis and glandular fever.

Spicer and his associates<sup>201</sup> have made the important observation that when rats are given sulfaguanidine (sulfamylguanidine) or sulfasuxidine (succinyl-sulfathiazole) in purified diets they show granulocytopenia or agranulocytosis and hypocellularity of the bone marrow. This condition can be largely prevented or treated successfully with dried whole liver or with certain liver extracts. In addition, the rate of growth of young rats is diminished, and occasionally anemia develops. The usual change in the blood, however, is a reduction in the total number of leukocytes with a decrease in the granulocytes, commonly to below 10 per cent. It has been suggested that these drugs produce the aforementioned effects by lowering the intestinal synthesis of certain factors essential to growth, or by direct toxic action or possibly by interference with the functioning of one or more enzyme systems in the animal body. The investigators conclude that it is possible that the direct toxicity, the indirect toxicity and the lowering of intestinal synthesis may all be involved. Beding<sup>202</sup> gives a critical review of present knowledge bearing on the problem of agranulocytosis.

#### INFECTIOUS MONONUCLEOSIS

Several important articles dealing with infectious mononucleosis have recently appeared, in which previous reports suggesting a virus as the etiologic agent are confirmed. In other publications it is urged that as the condition has many diverse

199 Curry, J. J. Acute Agranulocytosis Following Sulfadiazine, *J. A. M. A.* **119** 1502 (Aug. 29) 1942.

200 Mollison, W. M., and MacFarlane, R. G. Discussion on Throat and Nose Manifestations of Blood Disease, *Proc. Roy. Soc. Med.* **35** 401, 1942.

201 Spicer, S. S., Daft, F. S., Sebrell, W. H., and Ashburn, L. L. Prevention and Treatment of Agranulocytosis and Leukopenia in Rats Given Sulfamylguanidine or Succinyl Sulfathiazole in Purified Diets, *Pub. Health Rep.* **57** 1559, 1942.

202 Beding, A. Kritische Uebersicht über den heutigen Stand der Agranulozytose-probleme, *Med. Klin.* **38** 733, 1942.



manifestations the diagnosis must be based on the appearance of the characteristic lymphocytes in the blood and a positive antibody reaction against sheep cells, that jaundice, conjunctivitis and sometimes abdominal pain simulating acute appendicitis may appear as complications and that sulfathiazole and convalescent serum may be helpful therapeutic agents

Nettleship<sup>203</sup> has dealt with the puzzling question of the cause of infectious mononucleosis. According to him, there have been reports of unsuccessful attempts to prove the relation of various bacteria to the condition, but only one previous report has been made of the possible relation of a bacteria-free filtrate to the disease. According to van den Berghe and Liessens,<sup>204</sup> van den Berghe, Liessens and Kovacs<sup>205</sup> and van den Berghe and Liessens,<sup>206</sup> the agent is a virus, and this virus has been shown to produce the disease in monkeys. Furthermore, they state that freezing the virus appeared to increase its infectivity. The studies made by Nettleship may be summarized as follows. Sterile Berkefeld filtrates from nasal washings, as well as whole blood, from patients with the disease were inoculated into the chorioallantoic membranes of chick embryos, in a total of eight attempts to transmit the agent, positive results were obtained in 4, a continuation of the reaction through four to fourteen passages was obtained in about 50 per cent of the membranes, but the agent finally died out, unsuccessful attempts were made to transmit the virus to 25 mice by intraperitoneal inoculation, mononucleosis (prolymphocyte) could be produced in rabbits by the injection of a suspension of ground chick membranes, but it was not possible to obtain a positive heterophile reaction against sheep cells with the rabbit serum.

The clinical features of infectious mononucleosis are reviewed by McFarland,<sup>207</sup> who reiterates that the disorder is so common as to be almost endemic, yet one which is "seldom diagnosed" by many physicians and one associated with astonishing errors in diagnosis. The author has had to differentiate it from the following diseases: German measles, catarrhal jaundice, lymphatic leukemia, strangulated hernia and appendicitis. His chief reason for reviewing the characteristics of the disease is to emphasize the necessity of differentiating it from acute appendicitis. He raised the plausible possibility that the condition described as mesenteric lymphadenitis may not infrequently, or even always, be infectious mononucleosis. We must differ sharply with the author on one point, namely, his statement that "an occasional case runs a malignant and even fatal course." Patients with the disease may become severely ill, but in the event of a fatal termination considerable doubt is raised concerning the correctness of the diagnosis. In such cases the disease is usually some variety of leukemia, rather than infectious mononucleosis.

Ryan<sup>208</sup> stresses the fact that the protean nature of the clinical manifestations of infectious mononucleosis make the diagnosis uncertain unless a careful study

203 Nettleship, A. On Infectious Mononucleosis, *Proc Soc Exper Biol & Med* **49** 116, 1942

204 van den Berghe, L, and Liessens, P. Transmission de la mononucleose infectieuse humaine au *Macacus rhesus*. Resistance du virus aux basses temperatures, *Compt rend Soc de biol* **132** 90, 1939

205 van den Berghe, L, Liessens, P, and Kovacs, L. Transmission de la mononucleose infectieuse humaine au *Macacus rhesus*. Culture du virus en tissu, *Compt rend Soc de biol* **131** 156, 1939

206 van den Berghe, L, and Liessens, P. Transmission de la mononucleose infectieuse humaine (fièvre ganglionnaire de Pfeiffer) au *Macacus rhesus* et passages successifs d'un virus filtrant, *Compt rend Soc de biol* **130** 279, 1939

207 McFarland, J. E. The Clinical Problem of Infectious Mononucleosis, *J Iowa M Soc* **32** 10, 1942

208 Ryan, J. M. Infectious Mononucleosis, *Minnesota Med* **25** 871, 1942

is made of the blood and the atypical lymphocytes recognized, or unless the reaction against sheep cells is employed. A case is reported in which the disease constituted a diagnostic problem for the first two weeks of illness. During this time endocarditis, typhoid fever, undulant fever, acute cholecystitis and infectious mononucleosis were suspected. The cells characteristic of the disease did not appear until the eighth day of the illness, and the positive agglutination reaction was delayed until the twelfth day. The author warns that a negative reaction does not eliminate the diagnosis early in the course of the disease, and that one should keep in mind the fact that jaundice may be present.

Ash and Arbogast<sup>209</sup> report a series of 21 cases of infectious mononucleosis and review the literature in regard to this disorder. There was nothing unusual about their cases except that in 10 conjunctivitis was present, which caused them to stress the importance of this condition as a symptom. They emphasize that the appearance of a positive heterophile antibody reaction may be delayed. In 1 patient the reaction remained positive for a period of at least three months.

Some unusual manifestations of infectious mononucleosis are reported by Leavell and McNeel<sup>210</sup> in a series of 57 cases which they observed. They emphasize that commonly the clinical picture is so characteristic that the diagnosis is at once obvious but that atypical findings frequently occur and should be kept in mind when the observer is considering the diagnosis of this disease. Each of the 8 cases reported in detail had some unusual instructive feature, as follows: absence of all of the typical clinical features when the patient was first seen, a septic reaction with chills, fever and leukopenia, localized inguinal adenitis, a history of a tick bite, unexplained fever, a palpable spleen and agglutination of both sheep cells and *Proteus* X19 which suggested the diagnosis of Rocky Mountain spotted fever, symptoms which led to the removal of a normal appendix, fever, drowsiness, headache and changes in the spinal fluid which led to an erroneous diagnosis of encephalitis, jaundice.

Straus<sup>211</sup> emphasizes an important aspect of infectious mononucleosis which has not received the notice that it deserves, especially from surgeons. He reports the case of a patient who presented the signs and symptoms of acute appendicitis, for which she underwent appendectomy. The lesion in the lymphoid tissue of the appendix was found to be identical with the specific changes in the lymph glands in cases of infectious mononucleosis. These alterations, however, are not necessarily a constant finding, for in another case of infectious mononucleosis with the same complaints the appendix, by contrast, failed to reveal a similar lesion. In the case in which the appendix showed the characteristic lymphoid changes, the abdominal symptoms were considered to be greatly out of proportion to the degree of appendical involvement. The author concludes that no explanation is available for abdominal symptoms occurring in the course of infectious mononucleosis.

Sears<sup>212</sup> reports the interesting case of a 21 year old nurse who suffered from an attack of infectious mononucleosis of moderate severity. The only unusual aspect was a white blood cell count of 8,500 per cubic millimeter with 3 per cent polymorphonuclear neutrophils, 95 per cent lymphocytes and 1 per cent monocytes. This was noted on about the fifth day of the illness. There was also

209 Ash, H. H., and Arbogast, J. L. Infectious Mononucleosis, *J. Indiana M. A.* **35** 562, 1942.

210 Leavell, B. S., and McNeel, J. O. Infectious Mononucleosis. Unusual Manifestations, *Virginia M. Monthly* **69** 180, 1942.

211 Straus, R. Infectious Mononucleosis Simulating Acute Appendicitis with Description of a Specific Lesion of the Appendix, *Am. J. Clin. Path.* **12** 295, 1942.

212 Sears, W. G. Glandular Fever with Granulocytopenia, *Lancet* **1** 703, 1942.

mild anemia with the color index somewhat below 1.0, as well as slight anisocytosis, poikilocytosis and polychromasia of the erythrocytes, which gradually improved. By about the twenty-fifth day of the illness the leukocyte count was 5,300 per cubic millimeter with 40 per cent neutrophils. This increase followed injection of pentnucleotide but, in our opinion, was not necessarily due to it. It is well known that commonly there is leukopenia with a decrease in the leukocytes and an increase in the lymphocytes in the first week of this disease. Rarely, however, does it reach the extent observed in this patient.

Carlile and Blackford<sup>213</sup> report an interesting case which was regarded as one of infectious mononucleosis but in which there was the most unusual complication of severe anemia. They recognize that anemia in this condition usually casts a serious doubt on the diagnosis and suggests the possibility that the patient may be suffering from a more serious condition, such as leukemia. Nevertheless, the diagnosis in this case was indicated by the high titer of the agglutination of sheep cells, namely, 1:2,048. At the time the test was positive, the blood findings were as follows: hemoglobin content, 59 per cent (7.8 Gm), red blood cell count, 2,310,000 per cubic millimeter, leukocyte count, 7,800 per cubic millimeter, differential count, neutrophils 43 per cent, lymphocytes 56 per cent, eosinophils 1 per cent. The lymphocytes were reported to be of a type characteristic of infectious mononucleosis. Almost two years later the patient was reported as being in perfect health, although the blood was not examined at the time. It may be correct to state that this patient had infectious mononucleosis with the exceedingly rare complication of pronounced anemia, but it seems more probable that he had infectious mononucleosis with some other unrecognized cause for the anemia. There is a possibility the patient had acute lymphatic leukemia which went into remission and will eventually manifest itself again. In any event it is desirable that the authors record a complete follow-up note at some future date in order that the outcome of this important case may be recorded in the medical literature.

The case of a man aged 30 with the characteristic hematologic and clinical findings of infectious mononucleosis is presented by Magner and Brooks<sup>214</sup>. The atypical features which led to its being reported were hematuria, extensive presence of petechiae over the legs, with a few on the chest and buccal mucous membranes, an increased tendency to bleed from small cuts and oozing from the gums. Although the platelets were not counted, they are recorded as being greatly reduced at this time. The other blood findings were a hemoglobin percentage of 92 (Sahli), a red cell count of 4,950,000 per cubic millimeter and a leukocyte count of 18,800 per cubic millimeter with neutrophils 13 per cent, lymphocytes 77.5 per cent, monocytes 8.5 per cent and eosinophils 1 per cent. It was first thought that the patient had idiopathic thrombopenic purpura, but against this was the low percentage of neutrophils. The diagnosis of acute leukemia was unlikely because of the absence of anemia, furthermore, the lymphocytes, although of the type which may be found in leukemia, were much more suggestive of infectious mononucleosis. This observation led to a sheep cell agglutination test, and positive agglutination was found in the dilution 1:800. The patient, after being in the hospital for sixteen days, apparently recovered, examination two months after the onset showed the blood to be normal and agglutination positive only in the

213 Carlile, T, and Blackford, J. M. Infectious Mononucleosis, with Anemia, Skin Rash and Jaundice, *Northwest Med* **41** 137, 1942.

214 Magner, W, and Brooks, E. F. Infectious Mononucleosis with Acute Thrombopenic Purpura, *Bull Acad Med, Toronto* **15** 189, 1942, *Canad M A J* **47** 35, 1942.

dilution 1:10. One questions the diagnosis in this case because hemorrhagic manifestations other than epistaxis are exceedingly rare in infectious mononucleosis, as is a reduction in the number of blood platelets. Such cases have been regarded previously as instances of purpura haemorrhagica with an atypical white cell response. It is also possible that the patient had infectious mononucleosis but with it had also thrombopenic purpura due to some drug, such as one of the sulfonamide compounds or allylisopropylacetylcarbamide (sedormid).

The case of a patient in whom infectious mononucleosis followed catheterization of the ureter for hydronephrosis is reported by Feil<sup>215</sup>. The ailment was characterized by fever, leukopenia with 60 per cent mononuclear cells, a cutaneous rash, abdominal pain, inguinal adenitis and jaundice. The Wassermann reaction was negative, but the heterophile antibody reaction was positive in the dilution 1:30. It was suggested that the infectious agent entered through the urinary tract as a result of the ureteral catheterization. The cutaneous rash was thought possibly to have resulted from the administration of phenobarbital. Furthermore, the author considers the possibility that this drug might have lowered the patient's resistance to such an extent that the infection became established. To use the basis for these speculative suggestions does not seem sound.

Seeds<sup>216</sup> discusses the importance of acute cervical adenitis in children and the differential diagnosis of this condition and emphasizes that infectious mononucleosis should always be considered when acutely enlarged glands are observed in a child.

A review of present knowledge of infectious mononucleosis is given by Spark<sup>217</sup>. Smeall<sup>218</sup> reviews the historical, clinical, laboratory and therapeutic aspects of infectious mononucleosis with special emphasis on the sheep cell agglutination test. A complete bibliography is appended. A brief résumé of the symptoms and the laboratory findings of infectious mononucleosis, together with a report of a case in which the chief clinical manifestation was fever, is given by White<sup>219</sup>.

Comment is made by Martin<sup>220</sup> on jaundice as a complication of infectious mononucleosis (glandular fever). He had previously reported 2 cases in which it occurred, and in this communication, adds 3 more. In each instance bile appeared in the urine, but cutaneous evidence was absent. The diagnosis in each case was confirmed by a positive Paul-Bunnell reaction (agglutination of sheep cells). He states that frank jaundice is uncommon in patients with infectious mononucleosis but that daily testing of the urine would probably more often reveal latent jaundice. Carter<sup>221</sup> reports a case of jaundice complicating infectious mononucleosis because of its comparative rarity. He cites Martin's statement that only 18 instances have been recorded. His case was that of a woman aged 28 who had all of the classic clinical evidences of the disease, including the hematic changes and positive agglutination of sheep cells in a dilution of 1:256. One week after the onset, jaundice appeared and remained for thirteen days. It was thought to be of the obstructive type. The fact that the jaundice deepened as the peripheral glands continued to enlarge was in accord with Martin's theory.

215 Feil, L. Ein Beitrag zur Frage des lymphamoiden Drusenfiebers, Schweiz med Wchnschr **71** 1071, 1941.

216 Seeds, A. Acute Cervical Adenitis in Children, Texas State J Med **37** 592, 1942.

217 Spark, T. E. H. Infectious Mononucleosis, M J Australia **2** 413, 1942.

218 Smeall, J. T. Glandular Fever (Infectious Mononucleosis), Edinburgh M J **49** 291, 1942.

219 White, J. R. Infectious Mononucleosis. Case Report, U S Nav M Bull **40** 173, 1942.

220 Martin, L. Glandular Fever with Jaundice, Lancet **1** 153, 1942.

221 Carter, A. B. Glandular Fever with Jaundice, Lancet **1** 102, 1942.

that jaundice may result from enlargement of the glands in the portal fissure causing obstruction to the bile duct. Lymphatic leukemia and Weil's disease were considered in the differential diagnosis but eliminated by complete studies of the blood.

The case of a woman aged 20 with jaundice as a complication of infectious mononucleosis is reported by Gold<sup>222</sup>. On admission to the hospital she was regarded as having simple catarrhal jaundice, as she gave a history of nausea, vomiting and fever and was definitely icteric. If lymphadenopathy was present when the first examination was made, it was overlooked. The jaundice increased until the serum bilirubin amounted to 23.3 mg per hundred cubic centimeters of blood, and the icterus index was 150 units. The van den Beigh reaction was strongly positive. The true nature of the illness was ultimately disclosed by the finding of the characteristic atypical lymphocytes in the circulating blood and by the agglutination of sheep cells in a dilution of 1:128. According to this author, a majority of observers consider that jaundice in this condition is due to associated hepatitis, but Tidy attributes it to enlargement of glands in the porta hepatis.

In an editorial comment in the *Lancet*<sup>223</sup> it is emphasized that infectious mononucleosis may simulate many diseases and that, as jaundice may occur, the diagnosis of catarrhal jaundice may be seriously entertained. The advice is given that the diagnosis of infectious mononucleosis should be considered in connection with any disease that appears to be catarrhal jaundice but that shows some unusual features, especially adenopathy or splenomegaly.

Bornstein<sup>224</sup> reports an instance in which human serum was observed to contain sheep cell antibodies in high titer (1:1,600) despite the fact that the patient suffered from neither serum sickness nor infectious mononucleosis. Such a reaction, fortunately for the differential diagnosis of infectious mononucleosis, is exceedingly uncommon, probably because it is ephemeral and also because the antibodies disappear quickly from serum specimens stored in the ice box. It is somewhat surprising that increased titers of heterophile antibodies are not observed more frequently, as it has been shown that an ever increasing number of bacteria contain heterophile antigen. Among such bacteria are the Shiga bacillus and several pneumococcus and Salmonella types. Occasionally positive reactions have been reported in cases of gonorrheal septicemia, aplastic anemia, scarlet fever, rubeola, tuberculosis and filariasis and after injections of liver extracts. Such positive reactions, however, must be exceedingly rare, that they do occur is evidence that there is some relation between heterophile antibodies in human serums and infections. In Bornstein's case, which gives support to this conception, a strain of *Bacillus coli* was cultured from the blood of a patient with severe cystitis. The patient's serum gave a positive heterophile antibody reaction (1:1,600), the antibodies concerned could be differentiated from the types observed in serum sickness and infectious mononucleosis and were of the Forssman variety. Unlike the antibodies in infectious mononucleosis, they disappeared rather quickly from the patient's blood, and the titer of serum kept in the ice box decreased rapidly. The Wassermann reaction was positive temporarily, although the Kahn and Kline reactions were negative. There was a transient increase in isoagglutinins. The antibodies in such cases are, according to the author, the same types as those encountered in normal serums, and this, according to him, makes it probable that there is a relation between the fluctuating titers of these antibodies and infections.

222 Gold, S. Glandular Fever with Jaundice, *Lancet* 1:103, 1942.

223 Annotations, *Lancet* 1:112, 1942.

224 Bornstein, S. Heterophile Antibody Reaction Caused by Bacterial Infection, *Ann Int Med* 16:472, 1942.

Straus and Bernstein<sup>225</sup> have made an investigation of the five different techniques for the demonstration of the sheep cell agglutinins in the blood serum of patients with infectious mononucleosis. According to them, each of the following factors has an important effect on the sensitivity of the test: the amount of blood serum employed, the serial dilution of the serum, the concentration of the sheep cell suspension added to the serum, the temperature at which the mixtures are maintained. After a careful serologic study of a large number of patients with and without infectious mononucleosis, they conclude that series determinations are of more diagnostic value than single determinations and that the "single tube test," introduced by Straus in 1936, is of diagnostic value when positive but does not exclude the disease when negative. They state that increased titers of heterophile agglutinins had been reported for the blood serums of patients with serum sickness, pneumonia, scarlet fever, measles, tuberculosis, filariasis and aplastic anemia and for those of patients treated with quinine or parenteral liver extract. In the authors' limited experience they have been unable to confirm these claims, although the agglutination titers were high in a case of serum sickness. They consider that the differential absorption test is of diagnostic value, especially in cases of infectious mononucleosis, cases in which borderline titers of heterophile agglutinins are met with, and cases with a history of injections of horse serum.

Loneragan<sup>226</sup> reviews the development of present knowledge of the heterophile antibody reaction in infectious mononucleosis and discusses the Straus modification of the Paul-Bunnell test. It was concluded that a case cannot be classed as one of infectious mononucleosis on the simple or presumptive Paul-Bunnell test alone. By carrying out absorption tests on all serums yielding titers of 1:50 or higher with the presumptive test, the agglutinins may be correctly classified as agglutinins of serum sickness, of "normal" type or of infectious mononucleosis.

Canzani, Varela Fuentes and di Bello<sup>227</sup> discuss the serologic diagnosis of infectious mononucleosis and review present knowledge of the heterophile antibody test for the disease. As the disorder has varied clinical manifestations, this test is of value from a diagnostic standpoint. They warn that in some cases of infectious mononucleosis there may be a transient false positive serologic reaction for syphilis. They discuss the disease from the standpoint of etiology and consider the relationship of *Listerella monocytogenes* to the condition. In their opinion, the significance of this organism as a causative agent has not been demonstrated.

It is emphasized by Berkley<sup>228</sup> that as yet no successful treatment has been devised for infectious mononucleosis, despite the fact that in patients other than infants it constitutes a great handicap and makes for marked economic loss of time. The author treated 4 patients by intravenous injection of 100 cc of scarlet fever convalescent serum and observed complete clinical recovery in each within forty-eight hours. He states that these results bring up the following questions: Is the benefit due to a nonspecific action of human serum? If this is true, similar effects should be produced by pooled normal human serum. Is it possible that

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225 Straus, R, and Bernstein, M. T. Further Serological Studies in Infectious Mononucleosis, *Am J Clin Path* **12** 174, 1942

226 Loneragan, M. Straus Technique of the Paul-Bunnell Test, *Canad M J Technol* **4** 107, 1942

227 Canzani, R, Varela Fuentes, B, and di Bello, R. Reacciones serologicas de sífilis "falsas positivas" de la mononucleosis infecciosa (fiebre ganglionar de Pfeiffer), *Semana med* **2** 502, 1941

228 Berkley, H. K. Infectious Mononucleosis. Its Treatment with Scarlet Fever Convalescent Serum, *J Pediat* **20** 26, 1942

infectious mononucleosis is due to a member of the streptococcic group closely allied to the streptococcus of scarlet fever? Is 100 cc the correct dosage?

Smyth<sup>229</sup> reports the case of a young man with a severe attack of infectious mononucleosis who made a prompt recovery after receiving on four successive days 20 cc of serum from a patient convalescing from this disease. On the fourth and sixth hospital days 100 roentgens was applied locally to his throat. The only unusual finding in the case was a serum agglutination of typhoid bacilli in a dilution of 1:640, which the author concluded was due either to cross agglutination or to nonspecific stimulation of his typhoid antibodies. He had received typhoid vaccine three years previously. The agglutination of sheep cells occurred in a dilution of 1:356. It is difficult to evaluate the effects of treatment, and the final conclusion regarding the true efficacy of convalescent serum in this condition must await many more trials.

The effect of the administration of sulfathiazole in 7 patients with infectious mononucleosis was studied by Hoffman, Lees and Comroe<sup>230</sup>. It had been their experience that the usual measures employed in the treatment of this condition were disappointing and that the patients usually faced a long period of disability following the subsidence of the acute phase of the illness. A total dose of from 15 to 23 Gm was given to each patient over a period of six to ten days. The authors' limited experience did not warrant definite evaluation of this form of therapy, but the results attained appeared to be superior to those with other forms of treatment, since the fever, malaise, sore throat and much of the adenopathy disappeared after four to five days. The drug did not produce any appreciable change in the blood picture.

In a study of 29 patients with the disease whose serum gave agglutination of sheep cells, the highest white blood cell count was 26,400 and the lowest 3,700 per cubic millimeter, the only constant finding in the blood was definite lymphocytosis at some time during the disease. The clinical picture did not vary from that commonly observed, i. e., fever was present in 80.7 per cent, sore throat in 72.4 per cent, and general malaise in 72.4 per cent. Cervical adenopathy was noted in 100 per cent of the patients. The authors did not observe evidence of a person to person spread in any instance, nor did they have more than 1 case from the same fraternity house or dormitory at any one time. In conclusion it is stated that sulfathiazole produced prompt clinical improvement in the 7 cases in which it was used, without marked change in the white blood cell count or in the differential formula.

#### LYMPHOMATOID DISEASES, LEUKEMIA AND RELATED DISORDERS

*Hodgkin's Disease*—A series of 265 cases of Hodgkin's disease studied in the Memorial Hospital for the Study of Cancer and Allied Diseases, New York, has been analyzed by Slaughter and Craver<sup>231</sup>. The average survival time of the patients following the initial therapy was found to be thirty-three and eight-tenths months, and the average age of onset was 35 years. A predilection of the disease for males was observed in this study, and painless enlargement of the cervical lymph nodes was the commonest presenting symptom. Two regimens of roentgen therapy have been used in this clinic. The first, or "palliative," one

229 Smyth, L. A. Report of Case of Infectious Mononucleosis, Cincinnati J. Med 23: 292, 1942.

230 Hoffman, H. T., Lees, H. D., and Comroe, B. I. Use of Sulfathiazole in Infectious Mononucleosis, Am. J. M. Sc. 203: 731, 1942.

231 Slaughter, D. P., and Craver, L. F. Hodgkin's Disease. Five Year Survival Rate, Value of Early Surgical Treatment, Notes on Four Cases of Long Duration, Am. J. Roentgenol. 47: 596, 1942.



consists of moderate doses of roentgen radiation, sufficient to control symptoms, whereas the second or "obliterative" one aims at radical destruction of the disease cells wherever these are well localized. Five patients who had localized enlargement of lymph nodes were treated surgically, and excellent results were obtained in 3 of them. Although this group is too small to permit far reaching conclusions, the authors suggest that surgical procedures may prove of value in those patients in whom the disease is limited to a single chain of lymph nodes.

Haden and Burns<sup>232</sup> point out that, unlike lymphosarcoma and leukemia, Hodgkin's disease has never been reported in lower animals. Of their 47 patients, 10 complained initially of general symptoms, such as weakness, fever, loss of weight, anorexia and dyspnea, and the remaining 37 patients first noted lymphadenopathy, most commonly cervical. Splenomegaly occurred in 17 patients and hepatomegaly in 6. In 39 patients hypochromic anemia developed during the course of their illness. The total leukocyte count showed wide variation, but in general neutrophilia and relative lymphopenia and monocytopenia occurred whenever there was marked leukocytosis. The sexes were affected nearly equally, and the average age of incidence was 35 years. In this series the average duration of the disease was two and a half years.

In their survey of the osseous lesions of Hodgkin's disease, Vieta, Friedell and Craver<sup>233</sup> found at necropsy evidence of involvement of bones in 49 per cent of their 47 cases. In 257 cases the incidence of skeletal lesions demonstrable by roentgen examination was 14.8 per cent. Hodgkin's disease as contrasted with lymphosarcoma does not often include destruction of cortical bone. The pelvis, the vertebrae, the ribs and the femurs are most frequently attacked, with production of pain and local tenderness. A mixed osteoblastic and osteolytic lesion is characteristically found on roentgen examination, and the blood phosphatase level is elevated whenever osteoblastic reactions occur. The life expectancy in Hodgkin's disease has not been lessened by the presence of osseous lesions, according to these authors. The use of radiation has effected temporary improvement in many of their cases.

Zakon and Falkenstein<sup>234</sup> report their biopsy and necropsy observations in a case of mycosis fungoides. They believe that mycosis fungoides is a disease *sui generis* and can be differentiated from Hodgkin's disease by morphologic differences in the multinucleated giant cells (not clearly explained in this article) and by the absence of fibrosis in the lesions of mycosis fungoides. The infrequency of visceral lesions in mycosis fungoides and the dissimilarity of the dermal manifestations of the two diseases are substantiating arguments, these authors believe.

Wise<sup>235</sup> believes that by employing the Wintrobe method of determining the erythrocyte sedimentation rate valuable information regarding the activity of Hodgkin's disease can be gained. In 6 cases the rate was elevated whenever there was clinical evidence of progression. In 2 cases the rate was slowed just before death. In explanation the author refers to Wintrobe's statement that the erythrocytes of cachectic tuberculous patients may have a normal rate. He also suggests that inasmuch as these patients are severely anemic, the apparently low rate may be due to inaccuracy of the sedimentation correction factor.

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232 Haden, R. L., and Burns, J. T. Hodgkin's Disease. Review of Forty-Seven Cases, *Cleveland Clin Quart* **9** 144, 1942.

233 Vieta, J. O., Friedell, H. L., and Craver, L. F. A Survey of Hodgkin's Disease and Lymphosarcoma in Bone, *Radiology* **39** 1, 1942.

234 Zakon, S. J., and Falkenstein, A. P. Mycosis Fungoides. Report of a Case with Autopsy Findings, *Illinois M J* **82** 224, 1942.

235 Wise, B. The Sedimentation Rate in Hodgkin's Disease, *J Lab & Clin Med* **27** 1200, 1942.



Specific cutaneous lesions appeared initially in the case of Reimann, Havens and Herbut<sup>236</sup>. There was absence of superficial lymphadenopathy, although at necropsy enlarged abdominal nodes were found, which were histopathologically diagnostic of Hodgkin's disease. A nodular, ulcerated lesion of the rectum producing obstructive symptoms in a man 33 years of age was proved to be Hodgkin's granuloma, according to Spiesman and Rubenstein<sup>237</sup>.

Klawans<sup>238</sup> has reported the onset of Hodgkin's disease during the sixth month of pregnancy. The disease ran a rapid course in the 33 year old primigravida, and she died forty-five days after delivery. Parade<sup>239</sup> states that in his case of pregnancy complicated by Hodgkin's disease the child died shortly after delivery. No pathologic changes suggestive of Hodgkin's disease were found at necropsy. In his search of the medical literature he was able to discover no evidence pointing to transplacental transfer of the disease. Schwind and Hyde<sup>240</sup> report their findings in a 4 month old girl whose peripheral blood contained immature cells resembling lymphoblasts. The diagnosis of Hodgkin's disease was established on biopsy of a cervical lymph node. Bernreiter<sup>241</sup> found agglutination of the brucellas of undulant fever in the case of a male patient afflicted with Hodgkin's disease, although no further evidence of active infection with brucellas was obtained. The author wonders if brucellosis may produce a lesion resembling Hodgkin's disease.

*Lymphosarcoma*—In an excellent discussion of the malignant types of lymphoma Gall and Mallory<sup>242</sup> recognize seven distinct types (1) stem cell lymphoma, (2) clasmatocytic lymphoma, (3) lymphoblastic lymphoma, (4) lymphocytic lymphoma, (5) the lymphoma of Hodgkin's disease, (6) the sarcoma of Hodgkin's disease and (7) follicular lymphoma. The first four types possess a simple cytologic structure in contrast with the complex form of the remaining three types. From the analysis of their 618 cases the authors have found the onset of lymphoma to occur most frequently between the ages of 37 and 51 years. The lymphoma of Hodgkin's disease, lymphoblastic lymphoma and lymphocytic lymphoma occur with significant frequency in the first three decades of life whereas the clasmatocytic and follicular types afflict primarily the aged. Enlargement of the peripheral lymph nodes was found in 90 per cent of the entire series, while splenomegaly occurred most frequently with the lymphocytic type and least often with the sarcoma of Hodgkin's disease, stem cell lymphoma and clasmatocytic lymphoma. The highest incidence of osseous lesions was noted with the clasmatocytic type. Hematologic studies frequently demonstrated anemia of varying degree throughout the entire series of cases. Thrombocytosis was a common accompaniment of Hodgkin's sarcoma, and thrombopenia of lymphoblastic and lymphocytic lymphoma. The lymphocytic and the lymphoblastic lymphoma and the sarcoma of Hodgkin's disease often produce leukocytosis. Two

236 Reimann, H. A., Havens, W. P., and Herbut, P. A. Hodgkin's Disease with Specific Lesions Appearing First in the Skin, *Arch Int Med* **70** 434 (Sept) 1942.

237 Spiesman, M. G., and Rubenstein, H. I. Hodgkin's Lymphogranuloma (Rectal Stricture). Report of a Case, *Ann Int Med* **17** 349, 1942.

238 Klawans, A. H. Pregnancy Complicated by Hodgkin's Disease, *Am J Obst & Gynec* **43** 895, 1942.

239 von Parade, G. W. Diaplazentare Übertragung der Lymphogranulomatose? *Deutsche med Wchnschr* **68** 862, 1942.

240 Schwind, J. L., and Hyde, G. M. Hodgkin's Disease in an Infant. Report of a Case with a Peculiar Peripheral Blood Picture, *J Pediat* **21** 238, 1942.

241 Bernreiter, M. Hodgkin's Disease Complicated by Brucellosis, *J Kansas M Soc* **43** 330, 1942.

242 Gall, E. A., and Mallory, T. B. Malignant Lymphoma. A Clinico-Pathological Survey of Six Hundred and Eighteen Cases, *Am J Path* **18** 381, 1942.

years was the average duration of life for the entire series. The authors believe that judicious use of radiation as well as surgical treatment in certain selected cases may prolong life.

Stout<sup>243</sup> has studied 218 patients with lymphosarcoma, 156 of whom received roentgen therapy, surgical treatment or a combination of both. Of the treated patients, 21.8 per cent survived for five years and 14.8 per cent were symptom free at the end of this period of time. Only 3.2 per cent of the untreated patients lived for a similar length of time, and all of them had experienced recurrence of the tumor growth. It was observed that prolonged periods of survival were not obtained for patients afflicted with lymphosarcoma during the first three decades of life. Of the types of lymphosarcoma included in the series, the reticulum cell was found to be the most rapidly destructive. That favorable therapeutic results are attained only while the tumor remains localized is emphasized by this author. Jenkinson, Kinzer and Brown<sup>244</sup> are in agreement with Stout regarding the greater invasiveness of the reticulum cell sarcoma. Whereas their patients with lymphocytic sarcoma lived an average of forty-eight months after the onset of symptoms, the patients afflicted with reticulum cell sarcoma lived only twenty-four months.

Vieta, Friedell and Craver<sup>245</sup> discovered osseous lesions in 29 per cent of the cases of lymphosarcoma in which autopsy was done, and destruction of cortical bone frequently. These lesions, which were purely osteolytic, were widely disseminated over the entire skeleton and developed late in the course of the disease. Temporary improvement, amounting at times to complete regeneration of the bone, was observed after roentgen therapy.

Thirty-seven cases of tonsillar lymphosarcoma in which treatment was given at the Radium Institute of Paris, France, are reported by del Regato<sup>245</sup>. The earliest symptoms may be obstructive, inflammatory or metastatic. Following irradiation of the cancers, the details of which are included in the article, 40.5 per cent of the patients have survived from six to fourteen years without symptoms or signs of recurrence. Eight treated patients later had metastatic lesions of the cervical lymph nodes, whereas only a single patient had recurrence in the tonsillar area.

Two types of dermal reaction in lymphoblastoma cutis are recognized by Senear<sup>246</sup>. The first has the specific histologic pattern of the primary disease, and the second is a toxic manifestation of nonspecific character.

Interesting reports have been contributed to the literature by several investigators. Hine<sup>247</sup> presents his study of a 58 year old woman in whom a lymphomatous tumor of the left orbit developed. A lymphosarcoma of the lacrimal gland apparently cured by surgical removal and irradiation of the site is described by Perera<sup>248</sup>. Tenenbaum<sup>249</sup> was able to discover in the medical literature only 5 authenticated cases of lymphosarcoma of the prostate, to which he adds a report

243 Stout, A. P. Is Lymphosarcoma Curable? *J. A. M. A.* **118** 968 (March 21) 1942.

244 Jenkinson, E. L., Kinzer, R. E., and Brown, W. H. Lymphosarcoma, with Special Reference to the Reticulum-Cell Type, *Am. J. Roentgenol.* **48** 433, 1942.

245 del Regato, J. Roentgentherapy of Lymphosarcomas of the Tonsil, *Radiation Therapy, Tumor Inst., Seattle*, 1941, no. 2, p. 67.

246 Senear, F. E. Lymphoblastoma Cutis, *M. Clin. North America* **26** 1, 1942.

247 Hine, M. L. Report on a Case of Lymphoma of the Orbit, *Brit. J. Ophth.* **26** 297, 1942.

248 Perera, C. A. Lymphosarcoma of the Lacrimal Gland. Report of a Case with Giant Lymph Follicle Hyperplasia, *Arch. Ophth.* **28** 522 (Sept.) 1942.

249 Tenenbaum, J. Lymphosarcoma of Prostate and Epididymis. Case Report, *J. Urol.* **48** 113, 1942.

of a case The lesion is interesting inasmuch as some pathologists believe no lymph tissue exists in the prostate However, rudimentary lymph nodes have been described in prostatic tissue, and it is in all probability from one of these sites that the lymphosarcoma arose The presence of generalized lymphosarcomatosis in a patient who had congenital absence of the spleen is reported by Charache<sup>250</sup> Giant follicular lymphoblastoma of multicentric origin has been described by Held and Chasnoff<sup>251</sup> Involvement of both the spleen and the lymph nodes was noted in their case Jahsman<sup>252</sup> reports satisfactory remissions following roentgen therapy in a 53 year old man who had widespread follicular lymphoblastoma

*Leukemia*—Although no disease has proved more baffling and more discouraging to the clinician and the investigator than leukemia, there is no discernible slackening of interest in it In fact, the new investigational and therapeutic opportunities offered by the use of radioactive elements have acted as a powerful stimulus to workers in this field Recent studies concerning radioactive phosphorus will be discussed in a separate section

A statistical analysis of 64 cases of chronic myelogenous leukemia and 64 cases of chronic lymphocytic leukemia has been contributed by Pascucci<sup>253</sup> The average age of onset of chronic myelogenous leukemia was 41.1 years, and that of chronic lymphocytic leukemia, 49.6 years Males predominated slightly in the group suffering from chronic lymphocytic dyscrasia whereas an equal distribution with respect to sex was found in the group with myelogenous leukemia Almost half (44 per cent) of the patients suffering from myelogenous leukemia complained initially of symptoms related to splenomegaly, in contrast with those who had lymphatic leukemia, 63 per cent of whom noted progressive enlargement of peripheral lymph nodes at the onset and only 27 per cent of whom complained of symptoms related to enlargement of the spleen The average duration of life was two and five-tenths years in the group with myelogenous leukemia and two and eight-tenths years in the group with lymphocytic dyscrasia The author concludes that initial splenomegaly occurs in lymphocytic leukemia and early lymphadenopathy in myelogenous leukemia more frequently than was formerly supposed

In an analysis of 1,500 cases of leukemia in children Cooke<sup>254</sup> found the highest incidence in children of 3 and 4 years A sharp decline occurred during the following three years, followed thereafter by a more gradual decrease throughout later childhood Forty per cent of all the patients were between 3 and 5 years of age Approximately 60 per cent of the patients were boys The appearance of a peak of incidence during the third and fourth year is in contrast with statistics of other tumors of childhood, most of which appear with increasing frequency during later childhood On the other hand, the age incidence of childhood leukemia and that of childhood infections parallel each other closely For this reason and for the reason that leukemia often develops shortly after an acute infection, the author believes that such infections are one of the important factors in the production of these forms of blood dyscrasia in children

250 Charache, H Lymphosarcomatosis and Congenital Absence of Spleen, *New York State J Med* **42** 1363, 1942

251 Held, I W, and Chasnoff, J Giant Follicular Lymphoblastoma (Giant Lymph Follicle Hyperplasia), *Am J M Sc* **204** 232, 1942

252 Jahsman, W E Follicular Lymphoblastoma, *J A M A* **120** 1126 (Dec 5) 1942

253 Pascucci, L M Chronic Leukemia A Statistical Study of Symptoms, Duration of Life, and Prognosis, *Radiology* **39** 75, 1942

254 Cooke, J V The Incidence of Acute Leukemia in Children, *J A M A* **119** 547 (June 13) 1942

Four hundred and ninety-five cases of leukemia have been reviewed by Bethell<sup>255</sup> and have been classified into three main groups, the lymphogenous, the myelogenous and the histogenous, according to the type of parent cell involved. Lymphogenous leukemia has been further subdivided into the lymphocytic, lymphosarcoma cell and lymphoblastic types, myelogenous leukemia, into myeloblastic, myelocytic and myelomonocytic (Naegeli) types, and histogenous leukemia, into the histiomonocytic (Schilling) form. Of the types of acute leukemia, the lymphoblastic predominates during the first two decades, whereupon, after the age of 20, the myeloblastic gains ascendancy. The commonest type of chronic leukemia during the first six decades is the myelocytic type. After the age of 60 the lymphocytic type occurs with relatively increasing frequency. Acute monocytic leukemia was observed most commonly during the fourth and fifth decades, and chronic monocytic leukemia between the ages of 30 and 60 years without special predilection for any age group. Bethell believes that the incidence of acute leukemia may be actually increasing.

In a more detailed study of the lymphogenous (lymphatic) group, 190 cases were reviewed by the same author<sup>256</sup>. This group of cases comprised 43.8 per cent of all cases of leukemia studied at the Simpson Memorial Institute over a thirteen year period. There were 52 cases of lymphoblastic leukemia, 68 cases of lymphocytic leukemia and 70 cases of lymphosarcoma cell leukemia. The author considers the lymphoblastic dyscrasia as a "cataclysmic disaster of childhood," occurring most frequently in the first decade of life, predominantly in boys. The presenting symptoms were commonly those attendant on rapidly developing anemia, and the average life expectancy was only four months. Radiation therapy proved to be uniformly unsuccessful in these cases. Lymphocytic leukemia occurred under the age of 40 years in only 1 case, whereas lymphosarcoma cell leukemia showed no predilection with respect to age among females, although before the age of 10 years and after the age of 40 years it predominated in males. The most common initial sign of the lymphocytic and the lymphosarcoma cell leukemia was enlargement of the peripheral lymph nodes. The average duration of life of patients with lymphosarcoma cell leukemia was found to be one year in this series, in contrast with the four and nine-tenths years of the group of patients with lymphatic leukemia. Following irradiation of the lesions, a satisfactory, although temporary, remission of symptoms was the rule in the cases of lymphocytic leukemia, in contrast with the cases of lymphosarcoma cell leukemia, in which the results of roentgen therapy were generally less gratifying.

In their series of 22 cases of aleukemic paramyeloblastic leukemia, Evensen and Schartum-Hansen<sup>257</sup> found the duration of the disease to vary from two to fifteen months, with a more rapid course in younger patients. The ages of the patients ranged from 2½ to 71 years. Progressive normocytic or macrocytic anemia, thrombopenia and an elevated erythrocyte sedimentation rate were constant laboratory findings. The authors emphasize their findings of joint and skeletal pain. Splenomegaly was discovered during the course of the disease in 9 patients, whereas hepatomegaly occurred in 12 patients and lymphadenopathy in 9. Stomatitis was a late complication in 6.

255 Bethell, F. H. Leukemia. A Survey of Cases Observed Over a Fifteen Year Period, *Univ Hosp Bull, Ann Arbor* 8:65, 1942.

256 Bethell, F. H. Lymphogenous (Lymphatic) Leukemia. Diagnostic, Prognostic and Therapeutic Considerations Based on an Analysis of Its Morphologic and Clinical Variants, *J A M A* 118:95 (Jan 10) 1942.

257 Evensen, O. K., and Schartum-Hansen, H. The Symptomatology of Aleukemic Paramyeloblastic Leukemia, *Acta med Scandinav* 107:227, 1941.

That the first signs and symptoms of leukemia may be of ocular origin is emphasized by Hansen,<sup>258</sup> who presents a detailed discussion of the ophthalmologic changes in leukemia. Unfortunately, he presents no statistics concerning the relative frequency of the various abnormalities described.

A general review of monocytic leukemia has been contributed by Evans,<sup>259</sup> which is too lengthy to permit detailed discussion.

Dental journals have contained several interesting case reports in which the oral lesions of patients with leukemia have been discussed. According to Pasternack, Abbott and Werner<sup>260</sup> the presenting symptoms and signs may be (1) simple toothache, (2) swelling or hypertrophy of gingivae, (3) necrosis and ulceration of gingivae, (4) osteomyelitis of the jaw and (5) hemorrhages from the gingivae. A case of acute lymphatic leukemia is presented in which toothache was the earliest symptom of the blood dyscrasia. Armbrecht and Apple<sup>261</sup> report the case of a 32 year old man who had spongy, swollen gums which bled excessively. The hematologic findings were compatible with a diagnosis of lymphatic leukemia (probably acute, although not so stated). Mason<sup>262</sup> reports a case of chronic myelogenous leukemia in which severe gingival hypertrophy was a prominent feature. Similar findings in a patient suffering from acute monocytic leukemia were noted by Sagharian and Jones.<sup>263</sup> Mallett and Guralnick<sup>264</sup> point out the similarity of leukemic gingivitis and gingival hypertrophy caused by dilantin sodium (phenytoin sodium, sodium diphenyl hydantoin).

Hartz and van der Sar,<sup>265</sup> in their report on a patient who died of chloroleukemia, emphasize the unusually marked invasiveness of this variant of myelogenous leukemia. Pathologic examination demonstrated widespread invasion and destruction of the walls of blood vessels, formation of tumor thrombi and destruction of bronchial walls, as well as parenchymal infiltration of the kidneys and the pancreas. M'Glone's<sup>266</sup> patient, a 10 year old boy, presented bilateral orbital chloroma, which the author believes originally developed in the sphenoid sinuses. At autopsy green urine was found in the bladder. No detailed studies were made, however, to establish the nature of the urinary pigment.

That specific cutaneous lesions rarely occur in myelogenous leukemia is apparent in the study of Paul and Limaizi,<sup>267</sup> who were able to glean only 20 cases from the medical literature. They report a case in which indurated red nodules of the skin developed and in which improvement followed radiation therapy. Biopsy at a time when the peripheral blood was indicative of chronic myelogenous leukemia showed diffuse infiltration of the corium and subcutaneous tissues with masses of blast cells and occasional myelocytes. Shortly thereafter

258 Hansen, E. W. Eye Lesions in Leukemia, *Minnesota Med* **25** 580, 1942

259 Evans, T. S. Monocytic Leukemia. General Review of the Subject, *Medicine* **21** 42, 1942

260 Pasternack, J. G., Abbott, G. A., and Werner, R. D. Leukemia Gingivopathy. A Case of Acute Lymphatic Aleukemic Leukemia, *J Am Dent A* **29** 1193, 1942

261 Armbrecht, E. C., and Apple, C. A. Lymphatic Leucemia, *Am J Orthodontics* **28** 607, 1942

262 Mason, H. Gingival Hypertrophy Due to Myelogenous Leucemia, *Am J Orthodontics* **28** 738, 1942

263 Sagharian, L. M., and Jones, C. A. Acute Monocytic Leucemia. A Case Report, *Am J Orthodontics* **28** 561, 1942

264 Mallett, S. P., and Guralnick, W. C. A Case of Acute Monocytic Leucemia, *Am J Orthodontics* **28** 95, 1942

265 Hartz, P. H., and van der Sar, A. Chloroleukemia. Report of a Case with Special Reference to Its Neoplastic Nature, *Am J Path* **18** 715, 1942

266 M'Glone, J. A. A Case of Chloroma, *Glasgow M J* **138** 47, 1942

267 Paul, J. T., and Limaizi, L. R. Specific Cutaneous Lesions in Chronic Myeloid Leukemia. Clinical Significance, *Arch Dermat & Syph* **45** 897 (May) 1942

the leukemia entered an acute phase, in which numerous myeloblasts were found in the blood, and the patient soon died. Inasmuch as myeloblasts were found in the skin in large numbers at a time when the leukemic process was of a chronic type and the blood was practically devoid of these early cells, the authors suggest that there might well have been primary autochthonous cutaneous derivation of the myeloblasts from local reticuloendothelial elements rather than metastatic deposition of these immature cells in the dermis.

Chronic myelogenous leukemia occurring in a 6 week old boy has been reported by Poncher, Weir and Limarzi.<sup>268</sup> They believe this to be the youngest patient with the disease on record. Goehl<sup>269</sup> presents the clinical and hematologic findings in frank eosinophilic leukemia occurring in a lad of 18 years. Although the familial occurrence of leukemia is not common, Hornbaker<sup>270</sup> has been able to present a detailed account of 3 sisters with the disease. Two of them had lymphatic leukemia, and the third, myelogenous leukemia. All were middle aged. Four other siblings had no evidence of any blood dyscrasia, and there was no familial history of leukemia in preceding generations.

Farber and Bylebyl<sup>271</sup> point out that chronic lymphatic leukemia is rarely complicated by pulmonary tuberculosis, whereas the association of myelogenous leukemia and tuberculosis is not unusual. Three cases in which chronic lymphatic leukemia and active pulmonary tuberculosis occurred concomitantly are presented. An 83 year old patient of Richards and Moench<sup>272</sup> has been observed at intervals during the past sixteen years and has shown on each occasion hematologic abnormalities compatible with a diagnosis of chronic lymphatic leukemia. In a short article Sterne<sup>273</sup> describes and illustrates with photomicrographs the evolution of the monocyte. Brief reports of 5 cases of monocytic leukemia are included.

An antileukocytic sheep serum has been prepared by Thiersch,<sup>274</sup> who injected human myelogenous leukemic cells into these animals. The serum of the immunized sheep caused a strong febrile reaction six hours after its injection into patients with myelogenous leukemia. Both of these patients had previously had several courses of roentgen therapy and their leukemia had become refractory to this type of treatment. Forty days after the injection of the antileukocytic serum, further radiation was given, and a temporary clinical improvement followed.

Heinle, Wearn and co-workers<sup>275</sup> report a group of interesting experiments in which repeated injection of extracts from the urine of patients who had myelogenous leukemia into the tissues of young male guinea pigs produced myeloid hyperplasia and metaplasia. Soon anemia developed, followed by a marked increase in the leukocyte count. Concomitant with the leukocytosis, immature myelocytes and myeloblasts appeared in the peripheral blood. The animals appeared clinically

268 Poncher, H. G., Weir, H. F., and Limarzi, L. R. Chronic Myelogenous Leucemia in Early Infancy. A Case Report, *J. Pediat.* **21** 73, 1942.

269 Goehl, R. O. Eosinophilic Leukemia, with Case Report, *Journal-Lancet* **62** 252, 1942.

270 Hornbaker, J. H. Chronic Leukemia in Three Sisters, *Am. J. M. Sc.* **203** 322, 1942.

271 Farber, J. E., and Bylebyl, H. Lymphatic Leukemia and Tuberculosis, *Am. J. Clin. Path.* **12** 253, 1942.

272 Richards, G. G., and Moench, L. G. Chronic Lymphatic Leukemia. Report of a Case with Survival for Sixteen Years, *J. A. M. A.* **119** 632 (June 20) 1942.

273 Sterne, E. H., Jr. Diagnosis of Monocytic Leukemia from an Examination of the Peripheral Blood Stained with Wright's, with a Report of Five Cases, *Ohio State M. J.* **38** 234, 1942.

274 Thiersch, J. B. Antileukocytic Sheep Serum as Sensitizing Agent in Chronic Myeloid Leukaemia Refractory to Deep X-Ray Therapy, *M. J. Australia* **1** 225, 1942.

275 Heinle, R. W., and others. Myeloid Hyperplasia and Metaplasia Induced by Extracts of Urine from Patients with Myelogenous Leukemia, *Ann. Int. Med.* **17** 902, 1942.

ill and lost weight Necropsy demonstrated myeloid hyperplasia in the bone marrow and myeloid metaplasia in the spleen, the liver and the adrenal glands of the experimental animals No definite tissue response was observed in guinea pigs given injections of extracts prepared from the urine of patients with lymphatic leukemia Details of the methods of extraction are presented The authors believe that in the urine of patients who have chronic myelogenous leukemia there occurs an unknown substance capable of producing myeloid hyperplasia and metaplasia when injected into normal guinea pigs Miller<sup>276</sup> demonstrates lowered resistance to infection in guinea pigs similarly treated Small doses of an avirulent strain of staphylococci injected into guinea pigs previously treated with the extracts from the urine of leukemic patients caused a high mortality, whereas considerably larger doses of the same strain of staphylococci produced no reaction when injected into control animals

In their extended metabolic studies of spontaneous and induced leukemia of mice, Burk and co-workers<sup>277</sup> found no increase of anaerobic glycolysis in the lymph nodes with the induced leukemia This finding contrasted with the results of previous experiments conducted on lymph nodes of spontaneously leukemic mice On the other hand, the anaerobic glycolysis of leukemic mouse liver was considerably increased above the rate of control liver, and the leukemic liver tissue produced lactic acid whereas normal liver tissue consumed this metabolite In the Rf strain of mice the aerobic glycolysis of leukemic lymph nodes exceeded that of control tissue by as much as 50 to 100 per cent Hall and Furth<sup>278</sup> found no difference in the oxygen consumption of leukemic and normal mouse lymph nodes An inconstant increase of aerobic glycolysis was observed in leukemic lymph nodes, whereas anaerobic glycolysis was increased invariably

Interspecies embryonic transmission of avian leukosis was successfully performed by Pollard and Hall,<sup>279</sup> who employed the agent of fowl leukosis Leukosis occurred in duck, turkey, guinea fowl, pheasant and quail embryos That bone marrow of normal fowls becomes infective after explantation and in vitro cultivation in contact with leukotic plasma has been demonstrated in the experiments of Doljanski and Pikovski<sup>280</sup> They reported that the agent of fowl leukosis requires the presence of living cells in order to maintain its activity

Kirschbaum and Strong<sup>281</sup> believe that the efficiency of methylcholanthrene, 3,4-benzpyrene and 1, 2, 5, 6-dibenzanthracene in hastening the appearance of leukemia in the high leukemia F strain of mice bears a direct relation to the potency of these carcinogens in inducing other types of mouse tumors The experiments of McEndy, Boon and Furth<sup>282</sup> have demonstrated that roentgen exposure may act as a synergistic agent and increase slightly the incidence of

276 Miller, F R The Influence of Secondary Factors on Induced Leukemia, *J Clin Investigation* **21** 643, 1942

277 Burk, D, and others Metabolism of Induced and Spontaneous Leukemia in Mice, *J Nat. Cancer Inst* **3** 249, 1942

278 Hall, V E, and Furth, J Metabolic Studies in Mouse Leukemia The Metabolism of Lymph Nodes in Lymphoid Leukemia, *Cancer Research* **2** 411, 1942

279 Pollard, M, and Hall, W J Interspecies Transmission of Avian Leucosis in Embryos, *Am J Vet Research* **3** 247, 1942

280 Doljanski, L, and Pikovski, M Agent of Fowl Leukosis in Tissue Cultures, *Cancer Research* **2** 626, 1942

281 Kirschbaum, A, and Strong, L C Influence of Carcinogens on the Age Incidence of Leukemia in the High Leukemia F Strain of Mice, *Cancer Research* **2** 841, 1942

282 McEndy, D P, Boon, M C, and Furth, J Induction of Leukemia in Mice by Methylcholanthrene and X-Rays *J Nat Cancer Inst* **3** 227, 1942



leukemia in mice previously treated dermally with methylcholanthrene. A detailed account of the methods and of the histologic observations is presented.

Gardner<sup>283</sup> implanted pellets of estrone (theelin) in 303 mice of the CCB and C3H strains and subsequently observed the development of lymphoid tumors in 25 per cent of these animals. Tumors developed in only 2 per cent of 482 untreated animals. The neoplasms of the treated animals showed distinct predilection for the mediastinum and probably originated in thymus tissue.

Potter and Ward<sup>284</sup> studied the mitochondria of normal and leukemic mouse lymphocytes. They report that these structures appear as small discrete granules in supravital preparations of normal lymphocytes. In spontaneous and transmitted leukemia, the mitochondrial granules appear larger in size.

The leukemoid blood reaction is characterized as a vague category by Meyer and Rotten<sup>285</sup>. According to these authors, two types of reaction have been described. In the first type, although the leukocyte count remains normal or is but slightly elevated, examination of blood films reveals a high percentage of immature granulocytes. Marked leukocytosis is found in the second type of leukemoid reaction, but there is little evidence of granulocytic immaturity. Two cases of gastric carcinoma in which the second type of leukemoid reaction occurred are presented by the authors. Whittemore and Stich<sup>286</sup> observed a leukemoid reaction to sulfadiazine in a 34 year old woman in whom lobar pneumonia developed following an episode of diabetic coma. The leukocytes rose to 90,000 at a time when 37 Gm of the drug had been administered. Immature granulocytes were noted in the blood film. Following discontinuation of sulfadiazine therapy, recovery occurred.

An unusual case of myeloid metaplasia of the spleen associated with acute hemolytic anemia has been exhaustively discussed by Brewster and Wollenman<sup>130</sup>. The patient, a 25 year old white housewife, complained of weakness and pallor. She appeared icteric, and her spleen was enlarged. Laboratory studies revealed elevated bilirubinemia and hemoglobinemia as well as increased fragility of erythrocytes. The red cell count was 1,000,000 per cubic millimeter. After repeated attempts to demonstrate hemolysis had proved fruitless, splenectomy was performed. After this operation, profound anemia developed, and the patient died. Histologic examination of the spleen revealed many foci of myeloid metaplasia scattered throughout the organ. The authors believe that the spleen had been an important site of erythropoiesis and that its removal precipitated the demise of the patient.

*Polycythemia*—A 12 to 15 per cent increase of hemoglobin and erythrocytes was produced in the peripheral blood within a two week period, by the daily administration of 10 mg of amphetamine sulfate, according to Davis and Harris<sup>287</sup>. No effect was observed on the total leukocyte count, and there was no reticulocyte response. After the administration of the drug was discontinued, the blood values fell promptly to pretreatment levels. A similar rise of the erythrocyte and hemo-

283 Gardner, W. U. Lymphoid Tumors in Estrogen-Treated Mice, *Cancer Research* **2** 725, 1942.

284 Potter, J. S., and Ward, E. N. Mitochondria in Lymphocytes of Normal and Leukemic Mice, *Cancer Research* **2** 655, 1942.

285 Meyer, L. M., and Rotten, S. D. Leukemoid Reaction (Hyperleucocytosis) in Malignancy, *Am J Clin Path* **12** 218, 1942.

286 Whittemore, W. L., and Stich, M. H. Leukemoid Reaction to Sulfadiazine, *New York State J Med* **42** 1249, 1942.

287 Davis, J. E., and Harris, A. M. The Production of Experimental Polycythemia in Man by the Daily Administration of Amphetamine Sulfate, *Am J Physiol* **137** 94, 1942.



globin levels was observed by Davis<sup>288</sup> following daily injections of solution of posterior pituitary and of epinephrine hydrochloride in both normal and splenectomized rabbits and dogs. Since a significant response occurred in the splenectomized group, the author believes that the phenomenon is not caused by splenic contraction. It is believed that in both the human and the animal experiments these vasoconstrictor drugs cause a state of anoxemia in the marrow which stimulates the production of erythrocytes. Lowenhaupt<sup>289</sup> kept guinea pigs in a low pressure chamber for periods up to three weeks and noted an average increase of 1,000,000 erythrocyte cells per cubic millimeter of blood. He noted a definite rise in reticulocytes shortly after the animals were exposed to reduced oxygen tension, and studies made during this period demonstrated considerable hyperplasia of the marrow. When the animals were released from the chamber, the blood values fell to normal levels, this alteration being preceded by a decrease in the number of reticulocytes. During the period of recovery no increase of serum bilirubin or of tissue iron could be detected.

Although exhaustive experiments have proved beyond a doubt that continuous exposure to anoxia produces an elevation of blood erythrocytes and hemoglobin, relatively little work has been reported on the effect of intermittent exposure to anoxia. Stickney and Van Liere<sup>290</sup> studied the effect of intermittent anoxia on 5 dogs which were subjected to lowered barometric pressures simulating altitudes of 12,000 to 18,000 feet. The animals were placed in low pressure chambers for seven to nine hours daily over a period of six months, and the hemoglobin and red blood cell levels were determined at weekly intervals. The hemoglobin was the first to show an appreciable rise, this being noted first in the third week of the experiment. During the fifth week the erythrocytes showed a definite increase. An average increase of 74 per cent of hemoglobin and 84 per cent of red blood cells was observed by the end of the experimental period. These investigators conclude that intermittent exposure to anoxia is capable of producing a notable degree of acclimatization, proportional to the severity of the anoxia and to the length of time of exposure.

Of 11 patients treated for polycythemia with lead compounds, 9 have been reported by Falconer<sup>291</sup> to show satisfactory results. Repeated intravenous administration of lead phosphate was used. A tendency toward thrombosis constitutes a contraindication for this form of therapy. Lead acetate by mouth was found to be unsatisfactory, since damage to the liver, the central nervous system and the peripheral nerves was observed.

A toxic reaction to sulfonamide therapy occurring in a 61 year old man who had polycythemia vera resulted in anemia, leukopenia and neutropenia, according to Greenwald, Letwin and Spielholz,<sup>292</sup> who found that the polycythemic state returned after the bone marrow recovered from the intoxication. In a short article Rhodes and Grunberg<sup>293</sup> recorded a case of polycythemia vera with a

288 Davis, J. E. The Production of Experimental Polycythemia by the Daily Administration of Epinephrine or Posterior Pituitary Solution, *Am J Physiol* **137** 699, 1942.

289 Lowenhaupt, E. Recovery from Experimental Polycythemia, *J Lab & Clin Med* **27** 874, 1942.

290 Stickney, J. C., and Van Liere, E. J. Erythrocytes and Hemoglobin Values in Acclimatization Produced by Discontinuous Anoxia, *J Aviation Med* **13** 170, 1942.

291 Falconer, E. H. The Treatment of Polycythemia Vera with Lead Compounds, *Am J M Sc* **203** 857, 1942.

292 Greenwald, L., Letwin, J., and Spielholz, J. B. Toxic Effect of Sulfamylamide on the Hemopoietic Organs in a Case of Polycythemia Vera, *J A M A* **118** 975 (March 21) 1942.

293 Rhodes, A. J., and Grunberg, A. Polycythemia Vera with Low White Cell Count. *Brit M J* **1** 553, 1942.

leukocyte count of 5,500 cells per cubic millimeter. The data presented do not seem adequate to establish beyond doubt the diagnosis of Osler-Vaquez disease.

The infrequency of the association of polycythemia vera and thromboangitis obliterans has been noted by Silbert,<sup>294</sup> who presents his findings in such a case. The author does not believe that there was any cause and effect relation but that the two diseases occurred purely coincidentally. Polycythemia vera complicated by the development of Huntington's chorea was observed by Kotner and Tritt.<sup>295</sup> Multiple cerebral thrombi were believed responsible for the manifestations of involvement of the central nervous system. Fitz, Walker and Branch<sup>296</sup> present a lengthy and rather detailed account of the course of polycythemia vera in a middle-aged physician who was under their observation for several years. This patient was treated with a solution of potassium arsenite (Fowler's solution) and a low iron diet for an extended period with only moderate improvement. Subsequently spray irradiation of the entire body produced an excellent remission. Death eventually occurred, following coronary thrombosis.

*Effect of Radioactive Phosphorus in the Treatment of Leukemia, Lymphoblastoma and Polycythemia*—Radioactive phosphorus ( $P_{32}$ ) has now been employed in the study and treatment of leukemia, lymphoblastoma and polycythemia for three years. Although it is too early to attempt a formal evaluation of the merits and the limitations of this agent, several interesting preliminary surveys of therapeutic results have been published during the year.

Low-Beer, Lawrence and Stone<sup>297</sup> have contributed an excellent general review of the therapeutic use of radioactive phosphorus. The methods of preparation and of administration of this element and a résumé of the results attained in the group of patients studied at the Crocker Institute are included. Two methods of oral treatment have been used. The first consists in administering large doses of radioactive phosphorus (6 to 10 millicuries) by mouth at irregular intervals, whereas the second and more recently developed method consists in giving frequent small doses (0.5 to 3 millicuries) every three days. Further clinical experience will prove which of these therapeutic regimens is the more effective.

Craver<sup>298</sup> points out the fallacy of attempting to treat leukemia, a widely dispersed disease, by means of localized radiation. With the use of roentgen rays of high voltage, much of the disease is left untreated. Spray irradiation of the entire body has proved an advance over older forms of therapy. However, the body's tolerance to this type of treatment is not great enough to enable one to take full advantage of the difference in sensitivity of normal and leukemic tissue. Since radioactive phosphorus is absorbed in high concentration by rapidly growing cancerous tissue, irradiation of the malignant cells is accomplished with a minimum of damage to the normal tissues. Provided that there is evidence of adequate erythropoiesis, Craver administers to his leukemic patient 70 to 150 microcuries of radioactive phosphorus per kilogram in five to seven daily doses. Whenever

294 Silbert, S. Thrombo-Angitis Obliterans and Polycythemia Vera, *J Mt Sinai Hosp* **8** 1021, 1942.

295 Kotner, L. M., and Tritt, J. H. Chorea Complicating Polycythemia Vera. Report of a Case, *Ann Int Med* **17** 544, 1942.

296 Fitz, R., Walker, B. S., and Branch, C. F. Polycythemia Vera. Report of a Case. *Arch Int Med* **70** 919 (Dec.) 1942.

297 Low-Beer, B. V. A., Lawrence, J. H., and Stone, R. S. The Therapeutic Use of Artificially Produced Radioactive Substances, Radiophosphorus, Radiostrontium, Radioiodine, with Special Reference to Leukemia and Allied Diseases, *Radiology* **39** 573, 1942.

298 Craver, L. F. Treatment of Leukemia by Radioactive Phosphorus, *Bull New York Acad Med* **18** 254, 1942.

deficient erythropoiesis occurs, the dose is reduced to 20 microcuries per kilogram. Thirty-eight patients were treated for leukemia by the author at Memorial Hospital, New York. Of 11 with chronic myelogenous leukemia, 8 were still alive at the time of his report, and satisfactory remission had been produced. Generally, less favorable results were noted in 11 patients who had chronic lymphatic leukemia, whereas no improvement was discerned in 3 who had acute leukemia. One patient with eosinophilic leukemia was benefited by this form of therapy.

Working in the same clinic, Kenney<sup>299</sup> believes that radioactive phosphorus is effective in the treatment of chronic myelogenous leukemia as shown by (1) the reduction of the leukocyte count to, or nearly to, normal, (2) the decrease in splenomegaly, (3) the absence of disturbance in erythropoiesis, (4) the reduction in numbers of myeloblasts and myelocytes in the bone marrow and (5) the absence of radiation sickness. When it was employed in 8 cases of chronic lymphatic leukemia, 5 patients showed definite diminution in size of the spleen and the peripheral lymph nodes whereas only 1 patient demonstrated a decrease in the total leukocyte count. The author urges that caution be used when radioactive phosphorus is administered to patients whose bone marrow is extensively infiltrated, since their tolerance for this form of therapy is poor.

The fractional or small dose regimen of treatment is preferred by Fitz-Hugh and Hodes,<sup>300</sup> who report the results of radioactive phosphorus therapy in 38 patients with assorted diagnoses. Of 8 patients with polycythemia vera so treated, 4 had excellent remission, 2 improved only slightly or not at all, and the other 2 patients were commencing treatment at publication of the report. Of 5 patients with chronic myelogenous leukemia, 2 showed a remission following treatment with radioactive phosphorus. Two of 4 patients with chronic lymphatic leukemia improved after treatment. Only 1 of 5 patients with Hodgkin's disease and 2 of 6 patients with lymphosarcoma showed any response.

Diamond and Warren<sup>301</sup> have treated 12 children for whom a diagnosis of acute leukemia was made. In 3 of them true remissions occurred subsequent to treatment with radioactive phosphorus. Four patients showed slight improvement. In the remaining 5 patients the course of the disease was uninfluenced. Detailed results of the use of radioactive phosphorus in 22 cases of lymphosarcoma are presented by Kenney and Craver.<sup>302</sup> Four of the patients attained excellent remissions of from nine to twelve months. No improvement was discernible in 10 patients. Partial remissions occurred in 4 patients, whereas 2 have had recurrences, which were controlled by further radioactive phosphorus therapy.

Since slight exposure to roentgen rays causes prompt changes in the peripheral blood, Low-Beer and Treadwell<sup>303</sup> were stimulated to study the early hematologic effects of the administration of minute doses of radioactive phosphorus. Using normal human subjects, these authors concluded that 0.006 to 0.009 microcurie of radioactive phosphorus per gram of body weight was sufficient to produce

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299 Kenney, J. M. Radioactive Phosphorus as a Therapeutic Agent in Malignant Neoplastic Disease, *Cancer Research* **2** 130, 1942.

300 Fitz-Hugh, T., Jr., and Hodes, P. J. Clinical Experience with Radio-Phosphorus in the Treatment of Certain Blood Dyscrasias, *Am J M Sc* **204** 662, 1942.

301 Diamond, L. K., and Warren, S. Treatment of Leukemia in Children with Radioactive Phosphorus, *Am J Dis Child* **64** 958 (Nov.) 1942.

302 Kenney, J. M., and Craver, I. F. Further Experiences in the Treatment of Lymphosarcoma with Radioactive Phosphorus, *Radiology* **39** 598, 1942.

303 Low-Beer, B. V. A., and Treadwell, A. deG. Clinical Studies with the Aid of Radio-Phosphorus. Early Effects of Small Amounts of Radio-Phosphorus on Blood Cell Levels, Uptake and Excretion, *J Lab & Clin Med* **27** 1294, 1942.

in the peripheral blood discernible changes, consisting of a transient rise and fall of the platelets and a slight deviation of the red cell and hemoglobin levels in no constant direction

Erf and Tuttle<sup>304</sup> present further experimental data concerning the fate of radioactive phosphorus in therapeutic doses after its absorption from the intestinal tracts of patients being treated for chronic myelogenous leukemia, chronic lymphatic leukemia and polycythemia vera. Most of the substance remained in the acid-soluble fractions of the erythrocytes, leukocytes and blood plasma during the first ninety-six hours. Radioactive phosphorus appeared early in the nucleoprotein of the erythrocytes and attained a maximum value at the end of the first forty-eight hours after administration, whereas the radioactivity of the phospholipids of the erythrocytes slowly increased during a twenty-one day period. The radioactive phosphorus content of the phospholipid and nucleoprotein fractions of the leukocytes increased only during the first ninety-six hours after ingestion. During the same period the radioactive phosphorus of the phospholipid fraction of the plasma rose while that of the nucleoprotein fraction decreased.

As the result of extensive studies performed on cyclotron operators, Warren<sup>305</sup> discovered that a few persons show marked fluctuations of their total leukocyte count following only a minimal exposure to the rays emanating from the cyclotron. Such fluctuations indicate instability of the bone marrow and constitute a contraindication to further exposure to the radiation.

*Multiple Myeloma*—In their study of 127 cases of multiple myeloma at the Mayo Clinic, Ghormley and his co-workers<sup>306</sup> emphasize the lack of pathognomonic symptoms. Backache was the commonest complaint, followed by weakness and loss of weight. Pathologic fractures occurred in 40.6 per cent of their series. The disease has an average duration of one year after the onset of symptoms. It occurred in males twice as frequently as in females, and the average age of onset was 54 years. Albuminuria occurred in 70 per cent and urinary Bence Jones protein in 68 per cent of these patients. An abnormal serum albumin-globulin ratio was found in a little over half of the cases. The consistent roentgen finding of punched-out areas of bony rarefaction is emphasized. Working in the same clinic, Marisette and Watkins<sup>307</sup> analyzed the hematologic data of 56 cases of multiple myeloma. The most characteristic changes were (1) anemia of moderate severity and of normochromic type, (2) tightly packed erythrocyte rouleaux, resulting in the so-called greasy blood smear, and (3) accelerated erythrocyte sedimentation. The authors describe the morphologic differences distinguishing myeloma cells from Marschalko plasma cells. Beizer, Hall and Giffin<sup>308</sup> list hyperproteinemia, hypercalcemia, autohemagglutination, Bence Jones proteinuria, retention of nitrogen and an anticomplementary reaction of the blood serum as important but not pathognomonic laboratory findings of multiple myeloma. The value of aspirated sternal marrow as an aid to diagnosis is emphasized. Although life insurance statistics state that multiple myeloma comprises 0.03 of 1 per cent of all tumors,

304 Erf, L. A., and Tuttle, L. W. Phosphorus Metabolism of Blood of Patients with Leukemia and Polycythemia, *Am J M Sc* 203:83, 1942

305 Warren, S. Blood Findings in Cyclotron Workers, *Radiology* 39:194, 1942

306 Ghormley, R. K., Pollock, G. A., Hall, B. F., and Beizer, L. H. Multiple Myeloma, *Surg, Gynec & Obst* 74:242, 1942

307 Marisette, L., and Watkins, C. H. Multiple Myeloma. Diagnostic Value of the Blood Smear, *Proc Staff Meet, Mayo Clin* 17:433, 1942

308 Beizer, L. H., Hall, B. E., and Giffin, H. Z. The Diagnosis of Multiple Myeloma by Sternal Aspiration, *Am J M Sc* 203:829, 1942

Preston<sup>309</sup> believes its incidence to be considerably higher than is indicated by these figures. A short case history is included in his article. Haines<sup>310</sup> presents a case of myeloma which developed in the pharyngeal tonsil of a 75 year old farmer.

#### BONE MARROW

The sternal marrow of 40 healthy adults was examined by Plum,<sup>311</sup> who records the average percentage distribution of the various stages of leukocytes and erythrocytes found. A description of the cells normally found in marrow is included. Reich and Kolb,<sup>312</sup> studying 26 normal persons, performed simultaneous punctures at two sites on the sternum and made counts of the elements found, using Wright's stain. Since considerable variation occurred in their results, the authors conclude that quantitative determination of marrow cells is inexact. Davidson, Davis and Innes<sup>33</sup> review two opposing theories of the erythropoiesis in pernicious anemia. The first theory is that the megaloblastic erythropoiesis of pernicious anemia is quite distinct from normoblastic erythropoiesis, whereas the second hypothesis contends that the megaloblastic marrow of that disease results from arrest of maturation and subsequent disappearance of the more mature erythrocytic elements from the marrow. In their studies of 12 cases of pernicious anemia, the authors observed prompt transformation of the marrow within six to ten hours after the initial injection of liver extract. Megaloblasts decreased in number while early normoblasts increased abruptly. No evidence of increased mitosis was noted. These investigators believe that their data support the theory that arrest of maturation occurs. On the other hand, Wilson,<sup>313</sup> who made somewhat similar studies on 2 patients, concludes that liver therapy prevents the further development of abnormal megaloblasts and permits normoblastic erythropoiesis to proceed. In observations of the marrow in cases of iron deficiency anemia, this author has found evidence that administration of iron stimulates all stages of erythrocytic maturation.

Beizer and Watkins<sup>186</sup> report that in 12 cases of aplastic anemia death occurred only in those in which the marrow showed marked depression of hemopoietic activity and relative lymphocytosis. In cases in which the marrow was hyperplastic, recovery was the rule. Mandell, Meranze and Meranze<sup>314</sup> discuss the bone marrow in various common types of blood dyscrasia from the standpoint of morphology.

The importance of aspiration of sternal marrow as a diagnostic aid in cases of multiple myeloma is emphasized by Beizer, Hall and Giffin,<sup>308</sup> who were able to verify the diagnosis in 8 of their 10 cases by this procedure.

An unusual case of fatal asthma is presented by Chafee, Ross and Gunn,<sup>315</sup> in which 22 per cent of the nucleated marrow cells were eosinophilic granulocytes. Eosinophilic infiltration of the lungs and of the myocardium was also described.

309 Preston, E. P. Multiple Myeloma, *J Florida M A* **29** 82, 1942.

310 Haines, M. A Metastasizing Plasma-Cell Tumor of the Pharyngeal Tonsil, *J Laryng & Otol* **57** 264, 1942.

311 Plum, C. M. The Composition of the Bone Marrow in Normal Adults. The Cells of the Bone Marrow, *Acta med Scandinav* **107** 11, 1941.

312 Reich, C., and Kolb, E. M. A Quantitative Study of the Variations in Multiple Sternal Marrow Samples Taken Simultaneously, *Am J M Sc* **204** 496, 1942.

313 Wilson, T. E. The Bone Marrow in Anaemia, *M J Australia* **1** 513, 1942.

314 Mandell, T. H., Meranze, D. R., and Meranze, T. The Clinical Value of Sternal Bone Marrow Puncture, *Ann Int Med* **16** 1180, 1942.

315 Chafee, F. H., Ross, J. R., and Gunn, E. M. Eosinophilia in Fatal Asthma. Studies of Bone Marrow and Myocardium, *Ann Int Med* **17** 45, 1942.

Blood containing malarial parasites was injected intraosteally into 9 uninfected persons in the experiments of Quattrin<sup>316</sup>. The parasites disappeared from the marrow within three hours after injection and could not be demonstrated in reticuloendothelial cells or in myelocytes. Clinical malaria developed in 6 of the subjects after an incubation period of nine days, a period longer, the author believes, than that usually noted after intravenous injection and suggesting that the marrow exerts some unknown action which delays the onset of clinical symptoms.

Employing aqueous extracts of rabbit marrow, Nettleship<sup>317</sup> produced in guinea pigs a rabbit myelocyte antiserum which when administered intravenously to rabbits caused prompt significant neutropenia in their peripheral blood. Post-mortem examination of the experimental animals demonstrated hyperemia, petechiae and actual necrotic areas in the marrow. The spleen was uniformly enlarged.

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316 Quattrin, N. Ricerche sull' inoculazione del parassita malarico per via intramidollare, Riv di malarol **20** 229, 1941.

317 Nettleship, A. Bone Marrow Changes Produced by Specific Antibodies, Am J Path **18** 689, 1942.

(To Be Concluded)

## Book Reviews

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**A Manual of Clinical Therapeutics A Guide for Students and Practitioners** By Windsor C Cutting, M.D. Price, \$4.00 Pp 609 Philadelphia W B Saunders Company, 1943

The title presents concisely the contents and purpose of this book. The diseases and symptom complexes discussed include almost everything encountered by a general practitioner that requires drugs and allied procedures for its proper management. The book is relatively small, small enough that it can be easily carried in the pocket or medical bag. It includes a brief presentation of definite procedures that are to be used for each clinical state without discussing their advantages or disadvantages. The therapeutic recommendations are brief and to the point. As would be expected, a satisfactory use of this book requires a thorough knowledge on the part of the reader of therapeutics, pharmacology, physiology and clinical medicine. A physician with this knowledge can benefit considerably from the use of this book, for he can appreciate the reasons for the procedures recommended and understand the incompleteness of some of the discussions. For example, the discussion of the "Care of the Teeth and Gums" is presented by the author in three sentences. "The teeth should be brushed daily, preferably at bedtime. Dentifrices are cosmetic preparations which promote the use of a toothbrush and may otherwise aid cleansing the teeth. Tooth powders and pastes are equally satisfactory." Prescriptions for two inexpensive dentifrices are then suggested. Obviously, this is a summary of the care of the teeth and gums as practiced by many persons, but it is a far from adequate presentation of the whole problem of dental care, an extremely important and neglected therapeutic problem. Nevertheless, such examples do not detract from the value of the book when it is used intelligently by well trained physicians as a source of concise, ready information. The diet lists, lists of poisons and antidotes, weight and growth charts, rules for dosages and other aspects of the writing of prescriptions, lists of clinical laboratory procedures, with the values of the normal variations, quantitative methods for controlling drug therapy, lists of drugs, with doses, and bibliography are among the other good features of the book. The author has limited the drugs and procedures recommended to those accepted by the Pharmacopeia of the United States, the National Formulary and New and Nonofficial Remedies.

For persons who want concise and ready information on therapeutics, the book rates highly among any of its sort. The material is indexed satisfactorily, and the data are easily found.

**Vascular Spasm Experimental Studies** By Alexander John Nedzel, M.D. Price, \$2.75 Pp 151, with 161 figures Urbana, Ill. The University of Illinois Press, 1943

Nedzel presents a summary of his experimental work on vascular spasm. He believes that a great number of diseases are due to disturbances brought about in an organ as a result of vascular spasm. Following the spasm of blood vessels, there results anoxia with associated local disturbances in metabolism and if prolonged permanent physiologic and anatomic damage. Endocarditis, gastric ulcer and multiple sclerosis are among the disease states discussed. The author presents evidence of having produced these states, or their equivalents, in experimental animals by vasospasm, pitressin having been the vasoconstricting agent used.

The reviewer is impressed by the lack of thoroughness of control studies and the rather sweeping clinical implications made as a result of artificial experimental observations. Graphs are presented in the chapter entitled "Splanchno-Peripheral Balance" to show how application of cold to the surface of the body produces a decrease in the temperature of the viscera and heat a rise in visceral temperature. In practically all instances there is relatively little time allowed for the reaction from one stimulus to wear off before the other is applied. One is impressed by the fact that the rise in visceral temperature after the cold stimulus is removed is not due to the heat applied shortly after the removal of the cold stimulus but a result of the mere removal of the cold stimulus. In every experiment illustrated graphically, cold was the first stimulus used. The author did not isolate culturally and identify precisely injected organisms which were "made" to lodge in certain tissues, e.g. the mitral valves, because of previous injury by vascular spasm. In spite of such criticisms the monograph should prove of interest to investigators engaged in the studies of vascular physiology and the effects of climate on the mechanism of disease.

## CARRIÓN'S DISEASE

### IMMUNOLOGIC STUDIES

CALDERON HOWE, M.D.

BOSTON

Carrion's disease is the name applied to the clinical disease entity caused by infection with *Bartonella bacilliformis*. The term includes both the severe anemic stage of the disease, Oroya fever, and the less severe eruptive stage, verruca peruana. In the regions where the disease is prevalent the term *la verruga* is used to indicate any form it may assume.

Many aspects of Carrion's disease in its various phases remain to be explained. Noteworthy among these is the immunologic sequence occurring in a human being during the course of infection. That a tangible immunologic response in the form of agglutinins does occur in some instances has already been demonstrated.<sup>1</sup> It has been the primary purpose of the present investigation further to define the limits of this immunologic response in relation to the course of the disease and to attempt to ascertain what part, if any, the presence of specific agglutinins may have in the long-standing acquired immunity which almost invariably follows infection.

It became evident that a possible approach to this problem might lie in determining by means of the agglutination test the level of humoral antibodies in the serum from a significant number of residents of regions where Carrion's disease is endemic. This group of subjects would of necessity have to include patients in all stages of this specific disease, with and without a past history of it.

A program of investigation has consequently been carried out in the regions near Lima, Peru, where Carrion's disease is endemic. The field work was confined solely to the valleys of the Santa Eulalia and Rimac rivers, most of the material coming from the valley of the former. The actual localities involved are indicated in figure 1. In addition to those patients studied in the field, a number were seen in various hospitals in Lima who had contracted their disease in endemic areas other than those already mentioned, thus broadening somewhat the scope of the clinical material.

It should be emphasized that even short residence in any of the endemic areas involves repeated exposure to infection, provided no steps are taken toward protection against the wild sandfly, which feeds on human beings and animals only at night. Of the three species of sandfly occurring in the verruca zones, namely, *Phlebotomus noguchi*, *Phlebotomus peruensis* and *Phlebotomus verrucarum*, the last-named is most probably the chief transmitter of the disease. Complete protection can be assured only by quitting before nightfall the rather narrow belt between about 800 and 3,000 meters above sea level where *Phlebotomus* occurs.

This investigation was financed in part from the Repayments Fund of the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School.

From the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School, Boston, and the National Institute of Hygiene and Public Health, Lima, Peru.

1. Howe, C. J. *Exper. Med.* 75: 65-75, 1942.



Occasional persons have contracted severe Oroya fever from even a single night's sojourn in these regions<sup>2</sup> It is thus obvious that all of the persons encountered in the present study had had definite and sometimes prolonged exposure to infection with *B. bacilliformis*

#### MATERIAL AND METHOD

A total of 203 residents of the endemic regions already mentioned were seen in the course of the present work. Included among them were persons with mild and with severe active Carrion's disease, in each of its several manifestations. A large part of them represented recent arrivals in the particular areas studied, the duration of their sojourn having been a matter of months or weeks, rather than years. Most of them were laborers on a new electric power project in the upper part of the Santa Eulalia river valley, still within the limits of the endemic area. All three species of sandfly occur in these localities, which are thus well

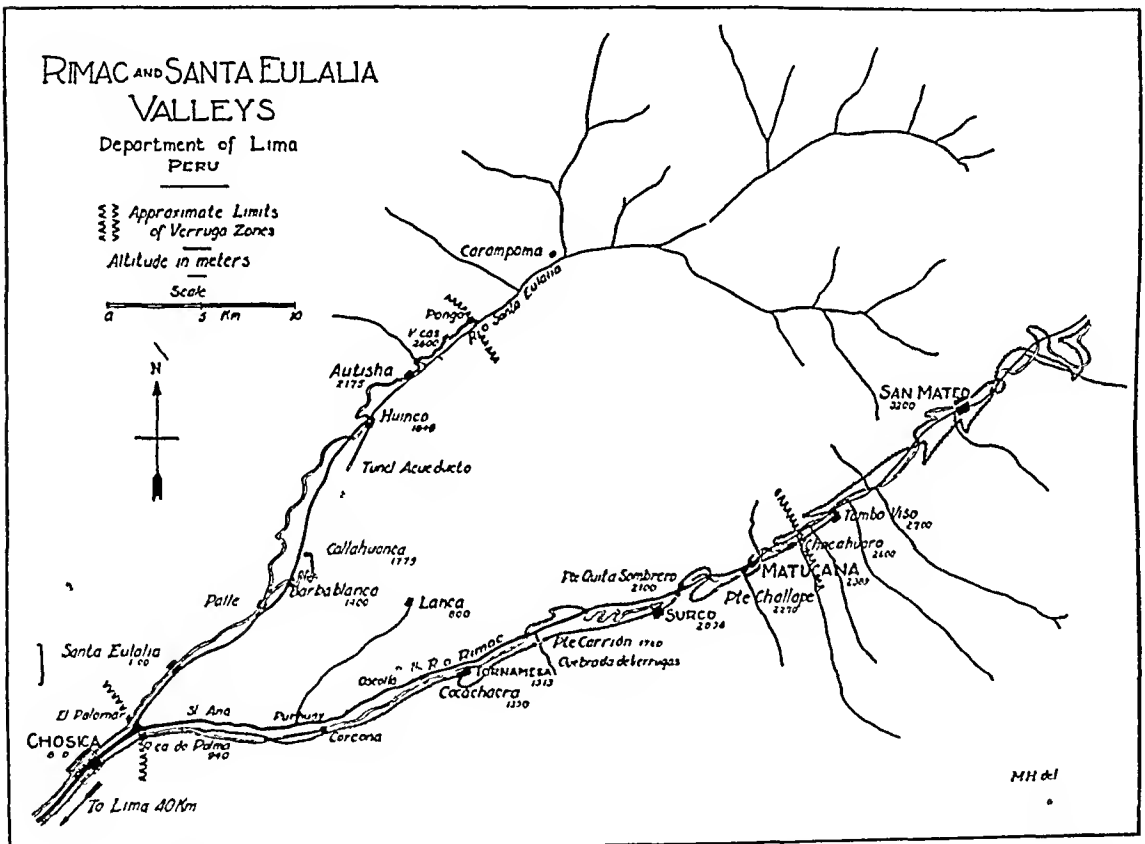


Fig 1—The area near Lima where the investigation reported here was carried out (from Hertig, M. *Am J Trop Med [supp]* **22** 1, 1942)

known centers of Carrion's disease. The remainder of the persons seen were longer term residents or natives of the two valleys mentioned and thus inevitably would have had prolonged exposure to infection.

Blood cultures were made for each patient, 5 to 6 drops of blood being inoculated directly into each of two tubes of German tryptone semisolid bartonella medium<sup>3</sup>. This medium was used exclusively during the field work, since it has proved itself to be far superior to leptospira medium both for primary isolation and for maintenance of *B. bacilliformis* in the laboratory. Blood for serum was taken at the same time from each patient. The level of hemoglobin was determined by the method of Sahli, the results being checked from time to time with ones obtained with an electric photocolormeter. The erythrocyte count, leukocyte count and hematocrit reading were determined when indicated, and a blood film was stained for *B.*

<sup>2</sup> Hertig, M. *Am J Trop Med (supp)* **22** 4-5, 1942

<sup>3</sup> German, Q. M. *Proc Soc Exper Biol & Med* **47** 329, 1941

bacilliformis with Giemsa's solution. Relevant clinical information was obtained in every case, with special emphasis on any past history of Carrion's disease, previous residence in endemic regions and possible evidence of actual infection. A physical examination was done whenever indicated, special note being made of the type and extent of any verrucous eruption.

The blood cultures were kept in the laboratory at room temperature ( $28 \pm 2^\circ \text{C}$ ) and examined with a binocular microscope (low power) after ten days to two weeks of incubation. At the end of this time in the tubes showing growth of *B. bacilliformis* the typical pearly white granular colonies were detectable in the strands of fibrin remaining from the original blood clot. All strains isolated from blood cultures were confirmed by dark field examination, were subcultured and have been carried through at least four transfers. They have also in many cases been transferred to Geiman blood agar<sup>3</sup> for determination of motility by dark field examination and for further morphologic and immunologic studies now in progress.

An agglutination test with *B. bacilliformis* was performed on serum from every patient within a period of not more than two weeks after the date on which the blood was taken. The antigen used had been prepared in Boston from stock laboratory cultures which had been maintained on Geiman blood agar. These cultures had originated from four different sources, as follows:

The first strain was isolated from the proboscis of a wild sandfly in 1939 in Peru by Dr. Marshall Hertig. The second originated from a patient with Oroya fever in Peru and was obtained by Dr. Q. M. Geiman in 1939. The third was isolated from a patient with severe Oroya fever in Colombia in 1940 and was obtained by Dr. Jose Jimenez Franco, of Lima. The fourth, from a patient with severe Oroya fever in Peru, I isolated myself in 1940. The reasons for the use of the four different strains in making up the antigen will be discussed later.

The antigen, as used, consisted of five days' growth of these four strains on Geiman blood agar. The organisms were washed off the slants, centrifuged and resuspended in a 0.4 per cent concentration of solution of formaldehyde U. S. P. in 0.85 per cent solution of sodium chloride, standardized to represent the growth of one slant per cubic centimeter of suspending medium.

The agglutination test has thus been modified by the substitution of a formaldehyde-treated antigen for the suspension of living organisms which was used in the test as originally devised. Formaldehyde treatment of the suspension was introduced at first chiefly as a measure of convenience, since it was felt that a well preserved and standardized antigen would give more consistent results. But it also afforded some coincidental observations of interest, which in retrospect substantiate the greater value of this type of antigen in testing unknown human serums.

In the original experiments,<sup>1</sup> in which suspensions of living organisms were agglutinated by serum of rabbits immunized with living organisms, the flocculus was coarse, heavy and tightly cohesive. Under the dark field microscope the large flakes of clumped organisms were easily demonstrated. In testing the agglutinating titer of immune rabbit serums used for therapeutic purposes during the present study (see appendix, table 1, patients 29, 190 and 205, and the footnote to table 1) a formaldehyde-treated suspension was used. The resultant flocculus was of much finer texture and more easily dispersed. Examined under the dark field microscope, the organisms were seen to be arranged in shreds rather than in clumps. Agglutination occurred at much higher titers with the formaldehyde-treated antigen than with the suspension of living organisms. In testing the human serums in the present series, for which the antigen was used, the flocculus in tubes with a strong reaction was identical microscopically and grossly with that obtained in testing immune rabbit serums with the same type of suspension.

An explanation for this difference in the character of flocculation with the two types of antigen might lie in the possibility that the formaldehyde-treated suspension represents a group-specific antigen, perhaps flagellar in origin and of a protein nature, since it reacts at higher dilutions of serum than does the living suspension. The latter may thus represent a type-specific somatic antigen.

It is possible that there exist several distinct strains of *B. bacilliformis*, characterized by different serologic specificity. Thus a formaldehyde-treated antigen, representing several of these strains, would be likely to react both with more serums and to a higher titer than an antigen prepared from a suspension of fresh, non-formaldehyde-treated organisms from a single source, i. e., a single strain. The strains included in the antigen which was used were chosen on an empiric basis, as already enumerated, and it was thought, a priori, that by so doing several different antigenic groups might have been included.

All agglutination tests were read after four hours' incubation at  $37^\circ \text{C}$ , followed by twelve hours' refrigeration, a hand lens with a power of 10 being used to examine the higher dilutions of serum. Agglutination tests were repeated on all serums after my return to Boston, with freshly prepared antigen identical with that which had been used in Lima. There were no discrepancies of any significance between the two sets of results. Slight agglutination in even

the lowest dilution of serum was considered of diagnostic significance in the light of the general results, and their correlation with the other aspects of the study, in the course of which serum from 35 persons without previous exposure to Carrion's disease failed to show any reaction. Included among these were 13 patients in a large Boston hospital.

### RESULTS

Of the whole series of 203 patients, 35.9 per cent showed definite evidence of clinical bartonellosis, either eruption or constitutional symptoms which were accompanied by blood cultures positive for *B. bacilliformis*. In this percentage were included 5 persons with typical Oroya fever. The serum from 18.7 per cent of the entire series of 203 subjects showed agglutination to varying titer, 3.0 per cent without clinical evidence of disease and 15.8 per cent with evidence of Carrion's disease, either the anemic stage with or without organisms visible in the blood smear or the eruptive stage. In 24.1 per cent of all the patients *B. bacilliformis* was demonstrated by blood culture, with or without accompanying disease or positive agglutination test. Past history of Carrion's disease was given by 30.6 per cent of all patients, 27.6 per cent without evidence of recurring or persistent disease. These results are summarized in the following tabulation.

Group and Table No	Blood Cultures *	Agglutination Test	Actual Carrion's Disease Eruption	Constitutional Symptoms	Past History of Carrion's Disease	Total Number of Patients in Group	Percentage of Series
1	+	+		+	—	16	7.9
2	+	+	+		—	9	4.4
3	—	+	+		—	6	3.0
4	+	—	+		—	15	7.4
5	+	—		+	—	3	1.4
6	+	5—, 1+	—	—	3+, 3—	6	3.0
7	—	+	—	—	3+, 3—	6	3.0
8	—	—	+	—	—	24	11.8
9	—	—	—	—	+	56	27.6
10	—	—	—	—	—	62	30.5
Number positive	49	38	54	19	62	203	100.0
Percentage of total	24.1	18.7	26.6	9.3	30.6		

\* Positive or negative for *B. bacilliformis*.

On the basis of the results of blood cultures and agglutination tests and the presence or absence of clinical disease or past history of it, all of the patients have been divided into ten groups, as indicated in the tabulation. The tables in the appendix at the end of this report show significant details in connection with the patients in each of these categories. In each case the age of the patient, the duration of the total period of residence in endemic regions and the locality or localities where this exposure to infection occurred have been noted. There is also in each case a brief summary of significant points in the history and in the clinical and laboratory observations.

In table 1 are included 16 patients (7.9 per cent of the total number), all of whom had blood cultures positive for *B. bacilliformis* accompanied by constitutional symptoms to greater or lesser degree. All of the patients in this group showed marked anemia, as indicated by red cell counts or hemoglobin level. In 5 instances this severe anemia was part of the picture of typical Oroya fever in that *B. bacil-*

hiformis was present in abundance in blood films. It is probable that the anemia in a number of other patients in this group might also have been the result of invasion of the blood stream, demonstrated only on blood culture. No organisms were encountered in routine blood smears of these patients, however, since the number of parasitized erythrocytes, if such there were, was too small to be immediately detectable. The patients with Oroya fever (patients 29, 190, 192, 196 and 205) showed a relatively lower titer of agglutinins than many of the other less severely ill persons in this group (patients 12, 141 and 194). Six patients (3, 12, 100, 121, 128 and 131) showed a significant rise in titer or increase in the strength of the agglutination reaction at constant titer on successive occasions during the course of their illness. The importance of this change in the titer is discussed in a later section. Carrión's disease developed in all of the patients in group 1 shortly after exposure in the endemic regions, and hence the periods of incubation had been relatively short.

The patients listed in table 2 (44 per cent of the total number) showed the typical clinical picture of *verruca peruana*, the later eruptive stage of Carrión's disease. The majority showed moderate anemia, less severe than that of the patients in the preceding group and in many instances due probably more to a general stage of malnutrition than to any specific infection. One patient (191) presented a history which in its time sequence is entirely consistent with earlier clinical Oroya fever followed by the typical eruption, here strictly confined in its distribution to areas of skin over joints. The serum from 4 of 9 patients agglutinated to a dilution of 1:160. It may be significant that in this group of patients with eruption the titer of agglutinins was higher in a relatively larger number than in the patients in the preceding group, who were in an earlier stage of the disease. The implications of this difference in titer are discussed later.

The patients in table 3 (3 per cent of the total number) differ from those in table 2 only in having blood cultures negative for *B. bacilliformis* on the single occasion on which they had been bled for serum. One such blood culture obviously did not mean that the blood stream had been consistently sterile. If several blood cultures had been made over a protracted period, it is more than likely that in this group one or more would have been positive for the parasite at one time or another. Four of these 6 patients had a titer of agglutinins of 1:160. It is of interest that 1 of these 4 (patient 204) had lived in endemic regions all of his life and presumably had thus been constantly exposed to infection, yet had no definite past history of any eruption suggesting Carrión's disease.

The patients listed in table 4 (74 per cent of the total number) had the typical eruption, and *B. bacilliformis* was recovered on blood culture. Their serums, however, showed no agglutination. These patients did not differ strikingly, either in duration or extent of disease, from those in table 3, yet agglutinins were not detectable.

The 3 patients in table 5 (14 per cent of the total number) had as a definite feature only their blood cultures positive for *B. bacilliformis*. They also showed symptoms of short duration, which may or may not have had some connection with the infection. It is thus conceivable that these 3 patients should be grouped with those in table 6.

Of the 6 patients in table 6 (3 per cent of the total number), 5 had only a blood culture positive for *B. bacilliformis*, 3 had a past history of typical eruption as well, and the serum from only 1 patient, who had no actual sign or past history of disease, showed agglutination. The patients in these two groups (tables 5 and 6), representing 44 per cent of the total number of persons studied might be called

"carriers" They were virtually asymptomatic, their disease being latent or past, but they still harbored the causative organism in the blood stream

In table 7 are 6 patients (3 per cent of the total number) for whom a positive agglutination test was the only definite evidence of specific disease. Three had a past history of typical eruption. Again it is possible that had several blood cultures been made in succession over a longer period, they might have been positive for *B. bacilliformis* on one or more occasions. In this respect these patients are analogous to those in table 3. Two of the 6 patients (65 and 68), being natives of the endemic regions, had had an eruption which may have been that of Carrion's disease and had an agglutination test positive to low titer. Whether this low titer had persisted since the original infection or whether it was the result of inapparent reinfection can only be a matter of speculation. It is possible that a positive agglutination test, in the absence of specific symptomatology, might indicate transient reinfection or a persistent carrier state not detectable by a single blood culture. On this basis, the patients in table 7 would increase the percentage of virtually asymptomatic carriers encountered among the total number of patients seen during the present survey to 7.4

The majority of patients with clinical disease had both blood cultures negative for the parasite and negative agglutination tests, as shown in table 8 (11.8 per cent of the total number). The data on these patients as to the period of exposure or type and extent of eruption do not differ essentially from the wide variety on patients showing blood cultures positive for the parasite and positive agglutination tests in other groups discussed (tables 2, 3 and 4). The average period of residence in endemic regions, and hence of exposure, of the patients in table 8 is three and five-tenths years. The average for the patients in tables 2, 3 and 4 combined is one and eight-tenths years. The variation among persons is so great, however, that these averages may mean little as a possible basis for explaining the absence of agglutinins in the serum of the group in table 8.

Tables 9 and 10 represent the majority of patients seen. Table 9 (27.6 per cent of the total number) includes all patients with only a past history of Carrion's disease, definitely established in almost every case. It may be of interest that the average duration of residence in endemic regions of the patients in this group is eleven and five-tenths years, far in excess of that of any of the other groups. They thus may represent the most commonly followed pattern in Carrion's disease: clinical disease, in wide variety, followed by lasting immunity against reinfection, without evidence of persistent agglutinins.

In contrast to these patients are those in table 10, representing 30.5 per cent of the total number of patients seen, in whose past history there was nothing to suggest clinically evident Carrion's disease, who showed no evidence of actual infection and whose blood was sterile to culture and did not contain agglutinins for *B. bacilliformis*. Presumably all of these patients had been more or less constantly exposed to infection, since they were all residents of endemic areas. To be sure, several patients in this group had not been exposed long enough to allow even for minimum incubation periods (i. e., patients 2, 27, 137, 142, 166, 167 and 203), and it is possible that these may later have come down with clinical disease or inapparent infection. It is impossible to say whether some of the patients in this group possessed a natural immunity or one acquired as a result of inapparent infection in the past. It is of interest that natural immunity to the disease seems to be possible even in the presence of inapparent infection (compare the patients in tables 5 and 6).

## COMMENT

*Clinical Data*—In the whole series there was wide variation in age among patients with different forms of Carrión's disease. It is probable, however, judging from the large number of persons in this series who had had past infection and who had resided in the endemic regions over a long period, that most natives contract the infection in some form in their earlier years, during which their first exposure takes place. The disease, in whatever form it may occur, does not seem to be more severe in one age group than in any other.

The majority of the patients were from the regions represented in the accompanying map, with a few from other endemic areas, such as Yauyos, Canta and Huaráz. There was no predominance of any one type of disease in any one region, since all types of eruption were encountered in both the Rimac and the Santa Eulalia river valley. Puente Carrión, also known as Puente Verrugas, is of historical interest in being one of the most notorious localities for contracting bartonellosis. This bridge is on the railway line from Lima to Oroya which passes through the Rimac river valley. During the construction of the railway 7,000 workmen are said to have perished, most of them of the severe anemic form of the infection, each crossing on the road costing a human life. This phase of the disease thus came to be known as Oroya fever.<sup>2</sup> Autisha is one of the highest points in the Santa Eulalia valley, where verruga is known to occur in abundance and where many of the patients mentioned here were seen (altitude 2,175 meters above sea level).

In the so-called "classic case" of Oroya fever the incubation period is thought to be ten days to three weeks.<sup>4</sup> The incubation period for the eruptive stage, with or without the anemic stage preceding it, varies much more widely and is not readily delimited. The actual incubation period for a given patient in the present series was difficult, if not impossible, to determine, since among the patients seen the duration of residence in the endemic regions, and hence of exposure, varied so greatly. There were many patients who had had but a few weeks to a few months of exposure in whom the severe form of the disease developed. On the other hand, there was 1 patient (table 1, patient 29) who had lived in the endemic region of the Santa Eulalia valley for eight years without sign or symptom before contracting severe Oroya fever. What factors determine the incubation period are not known. It is obvious that the duration of exposure bears no direct relation to the type or the severity of the ensuing disease.

The usual course of events is for one attack of Oroya fever or of verruga in any form to confer lasting immunity. Recurrence of Oroya fever is rare and was not encountered during the course of the present study. The recurrence of the typical eruption, however, is not uncommon. There were 4 patients with such recurrences in the present series (table 9, patients 48, 78, 84 and 106), 1 of them (patient 106) claiming to have had five attacks in all of typical verruga peruana. Whether these recurrent attacks represented acute exacerbations of persistent inapparent infections or actual reinfections is not clear.

Of great interest also were those persons with actual inapparent infection who harbored the organism, as shown by blood culture, but who were entirely asymptomatic or had only mild nonspecific complaints. A few had a past history of verruga, some with and some without a positive agglutination test. Such persons, along with patients with frank Oroya fever and verruga, may represent a natural reservoir of infection and serve as carriers to maintain the infection in wild sand-flies in a given locality or to carry infection from one site to another.

4 Rebagliati, R. Verruga peruana, Lima, Imprenta Torres Aguirre, 1940.

The symptoms which accompanied either form of the disease were variable when present. In the anemic patients, who also had usually moderate to marked elevation of temperature, there were symptoms characteristic of any anemia or fever, such as extreme fatigue, general prostration, dizziness, anorexia and thirst. Late in the anemic stage or early in the eruptive stage many patients complained of pain in the long bones and of severe arthralgia. The eruption, in many instances, was situated over bony prominences or over joints. One patient (table 2, patient 191), who presented a story entirely consistent with severe Oroya fever preceding his eruption, had nodules strictly confined to areas of skin directly over joints, large and small, of all four extremities. In other instances of extensive eruption the nodules were distributed at random, usually over the extremities and the face, and the miliary form on the trunk only. In the case of miliary nodules the eruption was often generalized.

*Blood Cultures*—The morphology of the various strains mentioned in the tables refers to observations made on second and third transfers from original blood cultures. It will be seen that there is a wide variety of growth characteristics, from large coarse granular colonies scattered at random throughout the medium to a fine cloudy type of growth confined to a sharp level usually in the upper 2 cc of medium. Often there were large granular colonies surrounded by a halo of satellite colonies. All of these strains were examined with the dark field microscope for the presence of motile organisms and spirals. It has been thought probable<sup>5</sup> that the presence and quantity of the fine rigid spirals often seen in the dark field microscope in large numbers loosely attached to colonies of organisms are an index of earlier motility of the strain in question. Actual motility is more easily demonstrated in young cultures on Geiman blood agar, to which a number of the new strains enumerated here have been transferred for further study. It will be seen that there is no correlation of the type of growth or the presence of spirals to the type, severity or duration of the clinical disease in a given case.

*Studies of the Blood*—In those patients with frank Oroya fever the degree of anemia was remarkably severe, in 3 cases (patients 29, 190 and 205) the erythrocyte count falling below 1,000,000 cells per cubic millimeter and the hemoglobin reaching extremely low levels. There was also severe anemia in the other patients with invasion of the blood stream demonstrated by blood cultures only and with marked constitutional symptoms (table 1). The type of anemia in these patients was usually normocytic or slightly macrocytic and hypochromic as judged by examination of a blood smear. It is difficult to explain the rather marked anemia encountered in some of the patients with eruption purely on the basis of persistent invasion of the blood stream by *B. bacilliformis*. Often, in addition, there was profuse bleeding from ulcerated and ruptured nodules, leading to marked secondary anemia. Malnutrition among the native population is prevalent to a degree so distressing that various deficiencies must be considered as playing a highly important part in the blood picture of all of the patients seen. Widespread occurrence of intestinal parasitic diseases, as well as malaria and tuberculosis, must also be counted among the many factors in this moderate to severe anemia encountered in the native population. It is of interest that marked leukocytosis was the exception in the present series and occurred in severe cases of Oroya fever usually only where there was definite evidence of serious secondary infection (table 1, patient 196).

*Agglutinins*—Among the chief objectives of the present study were the following ones to determine (a) at what stage during the course of natural infection

<sup>5</sup> Geiman, Q. M. Personal communication to the author.

with *B bacilliformis* there might be a rise in specific humoral antibodies detectable by means of the agglutination test, (b) how long these agglutinins persist after the peak of the infection and (c) whether agglutinins play any part in immunity

In an attempt to determine at what stage of the disease agglutinins appear, all of those patients showing definite eruption or constitutional symptoms referable to blood cultures positive for *B bacilliformis* with or without titer of agglutinins have been represented in the accompanying chart (fig 3), the titer of agglutinins where they occurred being plotted against the duration of the disease. Those patients not showing a titer of agglutinins are indicated in the separate strip underneath the main body of the chart. Each vertical line represents a single patient. The blood cultures made at the same time as the serologic tests are indicated as positive or negative, and each patient's illness is designated as eruptive, severely anemic (Oroya fever) or accompanied by constitutional symptoms. In only a few instances was more than one agglutination test on one occasion done during the course of a given patient's illness.

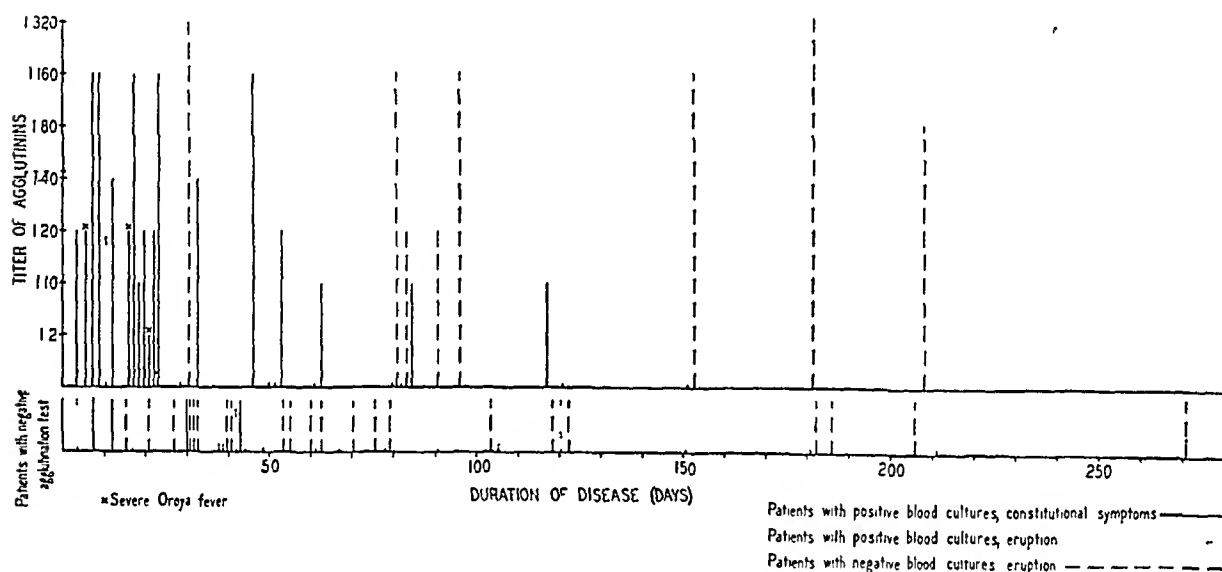


Fig 2—The relation of agglutinins for *B bacilliformis* to clinically evident Carrion's disease

Seventy-three patients are represented in the chart. Of these, 32.9 per cent had typical verrucous eruptions, early or late, with blood culture negative for *B bacilliformis* and negative agglutination test, 21.9 per cent had constitutional symptoms, chiefly those due to severe anemia (including 5 instances of proved Oroya fever, blood cultures positive for the parasite and positive agglutination test to varying titer), 20.5 per cent had positive cultures and negative agglutination tests but typical eruption, 12.3 per cent had positive cultures and agglutination tests and typical verruca, 8.2 per cent had typical verruca and negative agglutination tests and blood cultures, and 4.2 per cent had positive blood cultures, negative agglutination tests and constitutional symptoms probably due to proved infection.

It is obvious that no 2 cases would be exactly similar with respect to incubation period, duration of acute anemic stage or eruption. Rather the reverse was true in that there was wide variation in these factors, as far as they could be determined. They cannot therefore be exactly superimposed to give an accurate composite picture of the course of the disease as a whole. But it does appear likely, from the evidence as graphically outlined, that the majority of patients showed a



significant titer of agglutinins, often as high as 1:320, in the earlier stages of the disease. In other words, those patients who were tested during the anemic stage or during the first part of the eruptive stage were more likely to show significant titer than those patients who had recovered completely or who had had a minimal or extensive eruption over a relatively longer period. Of those patients in the earlier stage of the disease, either anemic or eruptive, showing moderate or high titer of agglutinins, by far the majority also had blood cultures positive for *B. bacilliformis*. The majority of these were either patients with severe anemia with organisms visible in the blood film or patients with severe constitutional symptoms explainable only on the basis of infection with *B. bacilliformis*, proved by blood culture. Of those patients showing a definite titer of agglutinins much later in the course of their disease, the larger part had blood cultures negative for the parasite and were in the eruptive stage. Though there are a few discrepancies between these two general categories, i. e., those early in the acute stage of the disease with positive blood cultures and positive agglutination test and those later in the course with eruption, negative blood cultures and positive agglutination tests, it appears likely that agglutinins, when they do appear, are detectable early in the acute stage of the disease, while blood cultures are still positive. They may persist into the eruptive stage after blood cultures have become negative. It should not be inferred, however, that blood cultures invariably become negative when the eruptive stage has developed, since in many cases organisms were recovered from the blood stream even after the eruption had completely subsided. The probability that agglutinins usually do not persist after the complete disappearance of the eruption is substantiated by data on the patients in table 9, all of whom had a past history of eruption or proved infection, with an average of five and nine-tenths years since the termination of disease. The only exception to this picture are 3 of the 6 patients represented in table 7 (patients 65, 68 and 162). These persons had past histories suggestive of verruga, as well as agglutinins to varying titer. For these patients it is impossible to tell whether the agglutinins had persisted since the original clinical disease or had reappeared as a result of more recent inapparent infection.

It is possible that in some of the infections of longer standing (table 7, patients 35, 39, 145 and 185) there might have been agglutinins earlier in the course of the disease. This is only speculation, however, and the only other conclusion to be drawn in the light of the evidence at hand is that in not all cases of even the most typical eruption is a measurable titer of agglutinins produced.

Conversely, it is unlikely that agglutinins play any significant part in the lasting acquired immunity which almost invariably follows the typical clinical disease. This is again evident from the patients listed in table 9. These all had had typical Carrion's disease in varying degree, which was apparently followed by lasting immunity, since in most cases there was no definite recurrence of eruption in spite of prolonged exposure by virtue of residence in endemic regions subsequent to the actual clinical disease. Recurrence of frank Oroya fever, as has been stated, is rare and was not encountered in the present study.

The question of the mechanism of immunity has been approached from another angle, that of active and passive immunization. Three patients with severe Oroya fever (table 1, patients 29, 190 and 205) were treated with a large quantity of hyperimmune rabbit serum of high agglutinin titer, prepared by repeated intra-

venous injection into rabbits of living *B bacilliformis*<sup>6</sup> The fact that these three attempts at passive immunization did not clear the blood stream of organisms is some indication that immunity to *B bacilliformis* is not of the rapidly sterilizing type

This possibility is also suggested by the preliminary results of another experiment<sup>7</sup> still in progress involving active immunization of persons without previous exposure to infection by *Bartonella* Twenty-two members of a military detachment, assigned to guard duty at three heavily infected localities in the Rimac river valley, were each given subcutaneously 1 cc of a formaldehyde-treated suspension of *B bacilliformis* (identical with that used in performing routine agglutination tests) before taking up their posts They were given 1 cc more after one week's tour of duty Three weeks to one month after the first injection all showed agglutinins for *B bacilliformis* There was no agglutination in any case or in any dilution with serum taken before immunization At the end of about five months of continuous residence in the endemic regions, none of the men showed any signs of severe illness, but from 11 of them *B bacilliformis* was recovered by blood culture The blood in every case before immunization and exposure had been sterile to culture It seems evident, therefore, that the production of specific agglutinins in human beings by inoculation with a formaldehyde-treated suspension of *B bacilliformis* does not in all cases prevent infection It appears possible, however, that such immunization might ameliorate the course of potential Carrión's disease in persons not previously exposed, since none of the group in question was incapacitated as a direct result of proved infection No final conclusions concerning the efficacy of active immunization in the prevention of Carrión's disease can of course be drawn until the data from these preliminary experiments on vaccination are completed and further application in the field is carried out

#### SUMMARY

A total of 203 inhabitants of two valleys on the Pacific slope of the Peruvian Andes in the foothills near Lima and natives of other parts who had come to Lima for hospitalization were examined for actual evidence or past history of Carrión's disease All were or had at one time been residents of regions where bartonellosis is endemic Blood cultures on special *Bartonella* medium were made for each person An agglutination test, using formaldehyde-treated suspensions of *B bacilliformis*, was performed on serum from each patient, once in Lima and again in Boston with freshly prepared antigen Routine studies of the blood were performed when indicated, with special emphasis on the possibility of encountering the specific organism in blood smears stained with Giemsa's stain

Important clinical data, including age incidence, geographic distribution, variety of symptomatology and types of disease encountered, are discussed in relation to pertinent laboratory studies Special emphasis is placed on the discussion of agglutinins and their role in acquired, active and passive immunity to infection with *B bacilliformis*

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6 Data on these 3 patients are to be reported in detail at a later date (Arch Int Med, to be published)

7 The experiment is being conducted in collaboration with Dr Marshall Hertig, of the National Institute of Hygiene and Public Health, Lima, and is to be reported in detail at a later date Dr Q M Geiman, of the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School, prepared and sent to Lima at short notice a portion of the vaccine used on some of the patients in this immunization experiment

TABLE 1—*Patients With Blood Culture Positive for B. Bacilliformis, Positive Agglutination Test and No Eruption or Past History of Carrion's Disease, but With Constitutional Symptoms*

Patient No	Age, Yr	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Blood Cultures	Agglutination Test						Comment	
					1	2	3	4	5	6		
3	32	3 mo, Puente Carrion	Pains in bones, headache, febrile symptoms for 5 wk, beginning 1 wk before end of period of exposure	A and B positive, varied granular growth, DF, no spirals	A 2 1 0 0 B 4 4 3	Studies of the Blood A R B C 2,530,000, hh 7.4 Gm. B R B C 3,540,000, hb 9 Gm						Laboratory data A at beginning of symptoms, B 1 mo later no eruption or marked fever
12	51	6 mo, Yauyos	Fatigue, "fever," and lethargy for 1 mo, climaxing about 2 yr of general ill health and vague complaints not accurately recalled	A and B positive large, granular colonies, sharp level	A 2 2 2 2 2 1 B 4 4 4 3 3 2	Seen in hospital, history of untreated chancre, Wassermann reaction +, Kahn reaction 4+, laboratory data A 23 days and B 45 days after onset of acute symptoms, 3 typical verrucose nodules developed 53 days after onset, death from generalized tuberculosis about 3 mo after onset of acute symptoms						
100	19	9 mo, Huinco	Pains in bones, occasional chills and fever for 2 mo	A and B positive, granular growth, DF, no spirals	A 0 0 0 B 2 1 0	A R B C 2,360,000, hh 7.25 Gm						First seen in field, later at hospital after admission with temperature of 103 F, laboratory data A in field, B 1 mo later on admission to hospital no eruption
111	24	2 mo, Puente Carrion	Temperature 101.8 F, pulse 120, general malaise, anorexia, pains in bones, loss of weight for 47 days preceded by 5 days of chills, fever and night sweats	Positive, DF, no spirals	2 2 1 0	R B C 2,850,000, hh 5.5 Gm						Extreme conjunctival pallor no jaundice sent to hospital 2 days after present data taken, no follow up
121	25	41 days, Puente Carrion	Malaise, "fever," night sweats and arthralgia for 2 mo	Positive, varied granular growth, sharp level, DF spirals	A 2 1 0 0 0 B 2 1 1 0	A hh 10.5 Gm. B hh 10.25 Gm						Laboratory data A after 2 mo of symptoms, B 2 wk later than A, symptoms having continued
123	29	3 yr (1923-1931), Huileno, 2 mo in 1933, Canta, 124 days prior to date of present data at Puente Challahe	Well up to 117th day of most recent period of exposure, when articular pains, malaise and nocturnal fever started	A positive, cloudy growth, DF spirals, B negative, C positive	A 0 0 0 B 3 3 2	A hb 9.5 Gm. B R B C 4,000,000, hh 9 Gm						Laboratory data A 105th day of most recent period of exposure, B 19 days later on 124th day of same period, C 70 days after end of period
131	24	110 days, Puente Challahe	Occasional chills and fever throughout period of exposure, temperature 99.4 F on 11th day and 100 F on 21st day after end of period of exposure	A cultures contaminated, B positive, granular sharp level, DF spirals	A 0 0 0 B 2 1 0 C 3 2 1	A hb 9.4 Gm. B hh 9.0 Gm						Laboratory data A 105th day of period of exposure, B 11 days and C 21 days after end of period
141	36	119 days, Puente Carrion	Arthralgia and pains in bones during last 3 wk of period of exposure	A positive, large granular colonies, sharp level, DF, no spirals	A 3 3 3 2 2 1 B 3 3 3 3 3 2	A hh 9.25 Gm. B R. B C 3,900,000, hematocrit reading 16						Laboratory data A 114th day of period of exposure, B 8th day after end of period 1 subcutaneous nodule on each knee 16 days after end of period

194	25	20 days about 1 mo prior to date of present data	Headache, malaise, febrile symptoms, pains in bones and anorexia for 1 wk	Positive, DF, many spirals	4 3 3 3 2 1	R B C 1,750,000, W B C 8,200, hb 4.75 Gm, hematocrit reading 26	Seen in hospital, treated with intravenous administration of glycerin, no follow up
200	24	92 days, Puentecarrón	Chills and fever on 84th day of period of exposure, anorexia and jaundice for 2 days	Positive, heavy granular level, DF, no spirals	3 2 1 1 0 0	R B C 3,590,000, W B C 8,100, hb 7.8 Gm	Seen in hospital, general symptoms improved, no follow up
70	41	26 mo, Calahuauca, Antischa	Three days of chills	Positive, large colonies, wide halos, DF spirals	3 2 1 0 0 0	Hb 9.75 Gm	Symptoms only suggestive of Carrion's disease
192	30	July 1941 8 days, Dec 1941 2 wk, Feb 1942 2 wk, Huaraz	15 days of fever, beginning with 1 chill, loss of weight, moderate icterus	A positive, B positive, cloudy level, C, positive, finely cloudy and granular growth, DF spirals	A 2 1 1	A R B C 2,050,000, hb 7.5 Gm, B bacilli forms in 28% of R B C, B R B C 2,070,000, hb 7.1 Gm*, C R B C 2,500,000, hb 7.75 Gm*, B bacilli forms in 70% of R B C	Seen in hospital, typical Oroya fever, laboratory data A 15th day, B 18th day and C 19th day of illness, from 14th to 25th day transfusion of 2,250 cc whole normal blood and 500 cc blood from person recovered from verruga, subsequent eruption and recovery with negative blood cultures 5 mo after onset
196	21	1 mo, Antischa	Vague illness lasting 3 wk	Positive, granular and cloudy level, DF spirals	2 0 0 0 0 0	R B C 1,740,000, W B C 10,600, hb 4 Gm, B bacilli forms in 78% of R B C	Seen in hospital, typical Oroya fever, died in 6th week of illness autopsy severe colitis of undetermined origin
29	51	8 yr, Calahuauca, Barabianca, Antischa	Sudden chills, fever and malaise for 18 days, jaundice for 2 days	A negative, B positive finely granular growth, DF spirals, D negative	A 0 0 0 0 0 0 B 4 1 0 0 0 0	A hb 11 Gm, B R B C 4,600,000, W B C 7,000, no organisms in smear, C R B C 1,430,000, W B C 9,300, hb 5 Gm*, hema tocrit reading 20, B bacilli forms in 25% of R B C	Seen in hospital, typical Oroya fever, laboratory data A 15 days before, B 13 days after, C 18 days after and D 2 mo after onset of illness treated with 50 cc anti Bartonella bacilliformis rabbit serum, recovery in 2 mo, no eruption
190	15	8 days ending 1 mo prior to present data, Rhuacriver valley, Matucana	Onset of fever, headache, malaise and jaundice 15 days after end of period of exposure	Positive, finely granular growth	4 4 1 0 0 0	R B C 610,000, W B C 14,000, hb 3 Gm*, hematocrit reading 8, B bacilli forms in 86% of R B C	Seen in hospital, typical Oroya fever treated with 60 cc anti Bartonella bacilli forms rabbit serum, mild erythema on 29th day of illness, complete recovery
205	21	6 mo ending 34 days prior to present data, Chinchipe	Onset of chill, headache, malaise, vomiting of coffee colored material and jaundice 13 days after exposure	Positive, finely granular growth, DF, no spirals	3 1 1 0 0 0	R B C 880,000, W B C 13,200, hb 3.25 Gm*, hema tocrit reading 10, B bacilli forms in 63% of R B C	Seen in hospital, typical Oroya fever, treated with 50 cc anti Bartonella bacilli forms rabbit serum, eventual recovery, with appearance of eruption 3 mo after onset of illness

A statistical analysis of the types of disease encountered, with relevant clinical and laboratory observations, is included in ten tables in an appendix at the end of this report. These serve to emphasize the wide variety of clinical and laboratory data encountered in a significantly large series of cases.

### CONCLUSIONS

From an analysis of the results of agglutination tests and blood cultures and the course of disease in each patient it becomes evident that a measurable titer of agglutinins is probably not produced in all persons with Carrión's disease. On the other hand, it appears that agglutinins, when they do occur, are detectable most often during the early acute anemic stage of the disease (clinical or sub-clinical Oroya fever), when blood cultures are regularly positive for *B. bacilliformis* and the parasite is often detectable in the blood smear. It may not be premature to conjecture that the titer of agglutinins encountered at this stage is proportional to the severity of the preeruptive invasion of the blood stream, and to the patient's response to such invasion as evidenced by the severity of symptoms and other relevant clinical data.

From observations made on several patients at different stages of their disease it is probable that the titer of agglutinins rises and most often reaches a peak just prior to the appearance of the eruption. As observed in the majority of cases in which eruption occurs, there is apparently a decline in titer as the eruption progresses and finally subsides. In the majority of cases after all evidence of eruption has subsided, no agglutinins are found in the serum. In many instances, blood cultures positive for *B. bacilliformis* may outlast the duration of the agglutinin response. Rarely is the reverse the case.

It appears unlikely that agglutinins play any major part in the almost universal acquired immunity which follows the typical clinical disease or in the apparent immunity which may be present in long term residents of endemic areas, who deny a past history of Carrión's disease.

Conversely, it appears improbable that the production of agglutinins for *B. bacilliformis* in nonimmune persons by active immunization with formaldehyde-treated vaccine prevents asymptomatic infection of the blood stream. Likewise, it is evident that administration of specific hyperimmune rabbit serum of high agglutinin titer does not sterilize the blood stream completely in cases of severe Oroya fever.

The agglutination test made with a formaldehyde-treated suspension of *B. bacilliformis* may be of some aid in the diagnosis of unexplained fever, anemia and constitutional symptoms, representing mild or severe illness preceding a later recognizable eruption in a person who is likely to have been exposed to infection. The agglutination test would not, however, seem to be of great use either in determining past infection or in estimating the degree of immunity in persons who claim to have had Carrión's disease.

Agglutination in even the lowest dilutions of serum is thought to be of diagnostic significance.

### APPENDIX

On the basis of results of blood cultures and agglutination tests and of the presence or absence of clinical disease or past history of it all of the patients studied have been divided into ten groups (see the tabulation in the text, paragraph 1 under "Results"). The data on all of the patients involved in the present study are compiled in the ten corresponding tables which follow.

TABLE 2—*Patients With Blood Culture Positive for B. Bacilliformis and Positive Agglutination Test, in Eruptive Stage of Carrion's Disease With or Without Constitutional Symptoms, But With No Past History of the Disease*

Patient No	Duration and Place of Residence		Clinical History, Signs and Symptoms	Blood Cultures	Agglutination Test						Studies of the Blood	Comment
	Age, Yr	Region			1	2	3	4	5	6		
5	50	8 mo., Autisha	Extensive eruption, large verrucomas present on arms, legs and face for 4 mo	Positive, granular growth	3	2	1	0			R B C 2,440,000, W B C 6,800, hb 75 Gm	Extensive hemorrhage from nodules, eruption still present 1 mo later
37	28	7 mo., Autisha	Scattered subcutaneous nodules and pains in bones present for 3 mo	Positive cloudy, sharp level, DF, spirals	2	1	0				Hb 10 Gm	
51	9	12 mo., Huileo	Generalized milary eruption for 3 mo	Positive, granular and cloudy level, DF, no spirals	3	3	2	0			R B C 3,060,000, hb 825 Gm	Eruption still present 5 mo after onset
177	23	10 mo., Puente Carrion	Fever, malaise, diarrhea and headache for 47 days, 1 cm nodule on right thigh for 1 wk	Positive, granular and cloudy sharp level	3	2	1	1	1		R B C 1,240,000, hb 375 Gm, hematocrit reading 14, no Bartonella in blood film	Seen in hospital, severe anemia, fever, no follow up
181	25	1 mo., Yauyos	Moderate sudammonous eruption for 3 wk, 1 subcutaneous nodule for 1 wk	Positive, scattered granular colonies, DF, spirals	4	3	3	2	1	1	R B C 1,240,000, W B C 8,500, hb 55 Gm, hematocrit reading 16	Seen in hospital, moderately febrile course no follow up
183	14	2 mo ending 5 mo prior to date of present data, Loya valley	Extensive confluent eruption on both lower legs, less on arms for 1½ mo, preceded by fever and minimal pains in bones at sites of eruption for 1 wk	Positive, fine granular growth, DF, spirals	3	1	1				R B C 3,470,000, W B C 7,200, hb 825 Gm, hematocrit reading 36	Seen in hospital, afebrile course
188	37	4 mo., Huaraz	One medium sized nodule for 2 mo preceded by severe constitutional symptoms	Positive, fine granular growth, DF, no spirals	4	3	2	1	0	0	R B C 4,330,000, hb 65 Gm, hematocrit reading 25	Seen in hospital
189	22	3 mo., Cahuahuana	One verruga, 1 subcutaneous nodule for 10 days preceded by vague general complaints	Positive, granular and cloudy growth, DF motility	2	2	1	1	1	1	No Bartonella in blood film	Seen in hospital, Kahn reaction 3+, Wassermann reaction —
191	14	2 yr., Yauyos	Extensive nodular eruption over all joints of extremities for 2 mo, preceded by constitutional symptoms, jaundice and pains in bones for 3 mo	Positive (subcultures contaminated)	2	1	1	1	1	0	R B C 4,000,000, hb 75 Gm, hematocrit reading 28	Seen in hospital, story consistent with Oroya fever followed by typical eruption, fever during 1st 3 days of eruption

TABLE 3—*Patients With Blood Culture Negative for B Bacilliformis and Positive Agglutination Test, in the Eruptive Stage of Carrion's Disease With or Without Constitutional Symptoms, But With No Past History of the Disease*

Patient No., Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Agglutination Test						Studies of the Blood	Comment
			1	2	3	4	5	6		
14 22 yr	1 yr., Autisha, Huineo	Eruption for 3 mo preceded by fever and pains in bones for 3 days, subcutaneous nodules on left ankle and forearm	3	2	1	0			R B C 4,360,000 W B C 6,600, hb 12.25 Gm	
122 32 yr	1 mo. a year prior to present data, Chaupichaca, 10 days prior to present data, Puente Carrión	Subsiding minimal miliary eruption present for 7 mo., preceded by febrile symptoms for 4 mo	A	0	0	0			B hb 11 Gm	Hands, arms and neck covered with sandfly bites, laboratory data: A after 10 days, B after 25 days and C after 36 days at Puente Carrión no change in clinical course
174 3 yr	Life, Paille	Eruption present for 6 mo., 1 cm nodules on legs and arms, preceded by febrile symptoms for 2 mo	3	2	2	1	1	1	R B C 2,390,000, hb 4.5 Gm, hema- toerit reading 16	Conjunctivas extremely pale
180 40 yr	4 mo., Huineo	Generalized miliary and nodular eruption present for 1 mo., preceded by generalized pains in bones and irregular fever for 2 mo	4	4	3	3	2	2	R B C 2,620,000, W B C 6,400 hb 7.75 Gm, hema- toerit reading 21	Seen in hospital, admitted 1 mo. prior to date of present data, slight fever during 1st few days, no fever thereafter
184 26 yr	9 mo. ending 5 mo. before date of present data, Yauyos	Eruption present for 5 mo., having appeared during last month of period of exposure, 1 large nodule on right arm, subcutaneous nodules on the shins	4	4	4	2	1	1	R B C 3,510,000, W B C 6,600, hb 8 Gm, hema- toerit reading 30	Seen in hospital moderately febrile course, with temperatures, not above 39 C (102.2 F) Kahn reaction 2+ Wasser mann reaction —
204 22 yr	Whole life save 6 mo. ending 10 mo. before date of present data, return to endemic region for 6 mo. ending 3 mo. before present data, Yauyos	1 nodule on right elbow, present for 16 mo., malaise, anorexia, pains in bones and night sweats present for 2 mo	3	4	4	4	3	1	R B C 2,600,000, hb 6.25 Gm	Seen in hospital

All periods appearing in any column in the tables are represented as ending on the date on which the data and blood for the present investigation were taken, unless otherwise specified in individual cases. Original blood cultures are labeled either positive or negative, according to whether typical growth of *B. bacilliformis* was detected grossly and confirmed by dark field examination after the proper incubation. The morphologic details mentioned refer to observations made on second and on third transfer from original blood cultures. All of these transfers were examined with the dark field microscope (indicated by "DF") and indication is given in each case where spirals or actual motile organisms were encountered. As mentioned in the text of this report, these spirals are thought to be an index of earlier motility of a given strain. The numbers 1 through 6 at the head of the column giving the results of the agglutination tests represent, respectively, final dilutions of serum, after addition of the antigen, of 1:2, 1:10, 1:20, 1:40, 1:80 and 1:160. The strength of the reaction in each case is graded from 4 to 0, 4 indicating a heavy flocculus with clear supernatant fluid, 3 to 1 indicating that agglutination was progressively less marked and 0 indicating that no agglutination occurred. A dash (—) indicates that no test was performed for a given dilution. Values for hemoglobin are expressed as grams per hundred cubic centimeters, and an asterisk indicates that a value determined by the method of Sahli was checked by means of an electric photocolormeter.

TABLE 4—*Patients With Blood Culture Positive for B Bacilliformis and Negative Agglutination Test, in Eruptive Stage of Carrion's Disease With or Without Constitutional Symptoms, But With No Past History of the Disease*

Patient No., Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Blood Cultures	Studies of the Blood	Comment
8 21 yr	7 mo., Autisba	Pain in bones for 4 mo eruption for 2 mo with small nodules on lower legs and 1 or 2 at each elbow	Positive, varied granular and cloudy level, DF, spirals	R B C 3,960,000, hb 10 Gm bematocrit reading 33	
10 27 yr	4 mo., Autisba	Recent eruption still present, 4 large subcutaneous nodules	Positive, granular growth, no level, DF spirals	R B C 3,290,000, hb 8 75 Gm	
19 27 yr	1 yr., Autisba	Eruption for 40 days with 2 nodules and 2 subcutaneous lesions, preceded by 1 wk of febrile symptoms	Positive, finely cloudy, sharp level, DF, spirals	R B C 4,670,000, hb 11 5 Gm	Eruption present 2 mo after present data taken
36 21 yr	9 mo., Huinco, Autisba	3 moderately large subcutaneous nodules and smaller scattered nodules present for 1 mo preceded by 1 wk of febrile symptoms and pains in bones	Positive, cloudy level, DF, spirals	R B C 3,970,000, hb 9 Gm	
45 30 yr	6 mo., Autisba	1 mo of slight malaise, small incipient subcutaneous nodules for 6 days	Positive, varied granular and cloudy, sharp level, DF, spirals	Hb 8 25 Gm	
54 19 yr	11 mo., Huinco, Autisba	Pains in bones for 1 mo and 1 subcutaneous nodule which subsided 7 mo prior to present data, general symptoms persisted	Positive, cloudy sharp level, DF, spirals	Hb 10 25 Gm	Infection probably extended over 7 mo
61 23 yr	7 mo., Huinco	2 wk of mild erythema on both lower legs and forearms, 2 days of fever 2 wk prior to eruption	Positive, fine irregular, bumpy growth no level, DF, no spirals	Hb 9 75 Gm	
73 2 yr	7 mo., Autisba	Eruption present for 2 mo, preceded by 1 wk of fever, anorexia and sweating, many small nodules, widely scattered	Positive, cloudy and granular growth, DF, spirals	R B C 3,970,000, hb 9 Gm	
74 23 yr	7 mo., Autisba	Eruption present for 3 mo, 2 subcutaneous nodules on left elbow	Positive finely granular sharp level, DF, spirals	Hb 9 25 Gm	
80 44 yr	1 yr., Autisba	Pains in bones of leg for 38 days, followed by minimal mild erythema on both wrists	A, B positive, varied granular growth, DF, spirals	A hb 10 75 Gm, B hb 10 5 Gm	Laboratory data A after 1 mo of symptoms, B 11 days later, 1 wk after eruption appeared
101 29 yr	1 yr., Barba blanca	1 subcutaneous nodule for 1 mo, preceded by 8 days of febrile symptoms	Positive, large and small colonies, with large halos, DF, spirals	Hb 9 Gm	Profuse bleeding from nodule
168 18 yr	8 yr., Santa Eulalia	Minimal mild erythema present on lower legs and forearms for 3 mo, preceded by febrile symptoms for 2 mo	Positive, varied granular and cloudy growth, DF, spirals		
182 30 yr	6 mo., Yauyos	Eruption present for 60 days, nodule on right knee and arm, legs covered with brownish vestiges of verrucous eruption, which had been preceded by vague febrile symptoms for 1½ mo	Positive, varied granular sharp level, DF, spirals	R B C 3,160,000, W B C 8,900, hb 8 25 Gm	Seen in hospital, schizonts and gametes of Plasmodium vivax in blood film chart unremarkable
197 19 yr	5 mo., Yauyos	Eruption present for 3 mo, subcutaneous nodules on lower extremities, preceded 4 mo earlier by irregular fever, ? jaundice, anorexia and splenomegaly	Positive, sparse finely granular colonies DF, no spirals	Hb 10 Gm	Seen in hospital, spleen palpable, hard, painful
15 25 yr	4 mo., Huinco, Autisba	2 to 3 subcutaneous nodules on arms and legs present for 2 mo, preceded by pains in the bones and night sweats for 2 mo	Positive roughly granular growth, DF, spirals	R B C 4,000,000, W B C 4,800, hb 12 0 Gm	In Huinco at time eruption appeared



TABLE 5—*Patients With Blood Culture Positive for B Bacilliformis and Negative Agglutination Test, With No Eruption or Past History of Carrion's Disease, But With Constitutional Symptoms*

Patient No , Age	Duration and Place of Residence in Endemic Region	Clinical History Signs and Symptoms	Blood Cultures	Studies of the Blood	Comment
77 29 yr	1 yr , Autisha, Huineo	1 wk of pains in bones of extremities and general malaise	Positive, finely granular growth, sharp level	Hb 9 75 Gm	
136 24 yr	110 days, Puente Challape	Headache and pains in bones for 3 to 4 days after end of period of exposure	A contaminated, B positive, DF spirals	A hb 9 25 Gm , B hb 9 25 Gm	Laboratory data A 105th day of period of exposure and B 11 days after end of period
179 45 yr	20 days at Huineo, ending 45 days before date of present data	Fever, generalized aches and pains, marked in legs, night sweats, weakness, diarrhea and epigastric pain for 1 mo	Positive, cloudy growth, indefinite level, DF, spirals	R B C 1 340 000, W B C 6,100, hb 4 75 Gm , hematoerit reading 14	Seen in hospital irregular moderately febrile course, with temperature not over 38.4 C (101.1 F) severe anemia B bacilliformis reported in smear earlier in course of illness, with erythroblasts and normoblasts

TABLE 6—*Patients With Blood Culture Positive for B Bacilliformis, Without Symptoms and With or Without a Past History of Carrion's Disease*

Patient No , Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Blood Cultures	Agglutination	Studies of the Blood	Comment
				1 2 3 4 5 6		
138 26 yr	110 days Puente Quita Sombbrero, Puente Carrion	? Pains in bones 1 mo after end of period of exposure	A positive, sharp irregular level, DF, spirals, B positive	A 0 0 0	A hb 10 5 Gm	Laboratory data A 105th day of period of exposure, B 1 mo after end of period
66 21 yr	Native of Yauyos, 3 yr in Huineo	No past history or actual symptoms of verruga	Positive, granular and cloudy level, DF, spirals	0 0 0	Hb 10 5 Gm	Reported as still asymptomatic 2 mo after present data taken
195 36 yr	1 mo at Puente Carrion 1½ yr prior to present data, at Puente Challape for brief period just prior to present data	Miliary eruption on arms, legs and face for 1 yr ending 6 mo prior to present data, occasional pains in bones, chills and fever to present time	Positive, 2 cloudy levels, occasional large colony, DF, spirals	0 0 0	R B C 3,570,000 hb 9 Gm	
7 36 yr	3 yr at Barba blanca, 10 mo at Autisha	Eruption for 8 mo 5 yr prior to present data 1 subcutaneous nodule on lower leg with minimal miliary eruption no signs or symptoms at time of taking data	Positive, DF, spirals	0 0 0 0		
72 30 yr	1 yr , Autisha	No past history of verruga, no actual signs or symptoms	Positive, coarse granular level, DF, no spirals	3 3 3 3 3 0	R B C 3 360,000 hb 7 25 Gm	
127 35 yr	Month of December 1939, Puente Challape, month of August 1941, Puente Challape, 1 mo prior to present data, Puente Carrion	Blood cultures positive 3 mo after sojourn at Puente Challape in August 1941, slight eruption on arms and legs of short duration no signs or symptoms since	A contaminated, B positive by DF	A 0 0 0 B 0 0 0	A hb 9 9 Gm , B hb 9 75 Gm	Laboratory data A end of month of last period of exposure, B about 1 wk after end of same period

TABLE 7—*Patients With Blood Culture Negative for B Bacilliformis and Positive Agglutination Test, With or Without a Past History of Carrion's Disease*

Patient No., Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Agglutination Test						Studies of the Blood	Comment
			1	2	3	4	5	6		
162 25 yr	3 yr, Santa Eulalia	2 yr prior to present data, extensive military eruption present for 4 mo preceded by 2 mo of constitutional symptoms and arthralgia, no signs or symptoms at present	2	2	1				Hh 10 25 Gm	
68 43 yr	Native of Canta	Verruga in childhood, with no details known, abdominal pain, anorexia, vomiting, loss of weight and irregular catamenia for 18 mo	2	0	0				R B C 2,000,000, hb 5 25 Gm, blood film quite suggestive of acute Oroya fever, no Bartonella	Seen in hospital, symptoms other than those of verruga, no diagnosis made urobilin in stool (3+), stool benzidine +
65 20 yr	Native of Matucana, 2 mo in Huineo	Minimal eruption preceded by 8 days of fever at 6 yr of age, no signs or symptoms since	2	1	1	0			Hh 9 5 Gm	
132 30 yr	110 days, Puente Challape	Vague febrile symptoms and pains in bones during last week of period of exposure, no past history of verruga	3	1	0				Hb 9 4 Gm	Cultures contaminated, no gross evidence of growth of Bartonella
134 30 yr	110 days, Puente Queta Sombrero, Puente Challape	No past history, signs or symptoms of verruga	3	3	2	1	0	0	R B C 3,700,000, hb 7 5 Gm	Cultures contaminated, no gross evidence of growth of Bartonella
64 40 yr	1 yr, Huineo	No past history, signs or symptoms of verruga	3	2	1	0			R B C 3,790,000, hb 9 Gm	

TABLE 8—*Patients With Blood Culture Negative for B Bacilliformis, Negative Agglutination Test, But With Actual Eruption, With or Without Constitutional Symptoms of Carrion's Disease*

Patient No.	Age, Yr	Duration and Place of Residence in Endemic Region	Type and Duration of Disease	
6	47	4 mo, Autisha	Sparsely scattered nodular eruption, 3 wk	
11	39	1 yr, Huaráz	B bacilliformis reported in blood film 2 mo prior to appearance of 1 nodule, no severe attendant illness	
17	19	8 mo, Huineo, Autisha	Three subcutaneous nodules, 2 mo	
20	31	8 mo, Autisha	Small subcutaneous nodules, right shin, 1 mo	
22	38	4½ yr, Barbablanea, Autisha	Military eruption, forearms and lower legs, 53 days	
23	26	9 mo, Autisha	Subsiding military eruption, 54 days	
30	31	1 yr, Huineo, Autisha, Barbablanea	Sparsely scattered nodules, with military eruption over both thighs, 2 mo	
35	18	7 mo, Autisha	Three subcutaneous nodules, 6 mo	
38	48	11 mo, Autisha, Huineo	One small red nodule, right wrist, 1 mo	
39	50	10 mo, Autisha	Varied nodular eruption, face and legs 6 mo	
47	19	4 yr, Huineo, Autisha	Sparsely scattered small nodules, 2 mo	
71	28	10 mo, Autisha	Minimal military eruption, extremities, 4 days	
75	34	9 mo, Huineo, Autisha	Several nodules, legs and arms, 2½ mo	
93	19	1 yr, Huineo	Three definite subcutaneous lesions, 2½ mo	
96	42	8 mo, Huineo	Moderate number of nodules, arms and legs, 8 days	
97	26	3 mo, Huineo	Moderate number of nodules, arms and legs, 26 days	
98	37	1 yr, Huineo	One or two subcutaneous nodules with numerous small nodules on forearms and lower legs and military eruption on arms and legs, 4 mo	
114	70	13 yr, Santa Eulalia river valley	Subsiding generalized varied nodular eruption, 7 mo	
145	28	Life, San Jeronimo	Evanescent military eruption over entire body, 1 yr	
176	17	137 days, Tornamesa, Sureo, San Mateo	Extensive generalized nodular eruption on arms and legs, 1 mo	
186	27	4 mo, Huineo, Autisha	Two subcutaneous nodules with generalized military eruption on arms and legs, 2 mo	
187	24	Life, Canta	Eruption 103 days	
185	20	1 mo ending 5 mo prior to present data, Yauyos	Generally scattered subcutaneous nodules, 5 mo	
198	22	3 mo ending 7 mo prior to present data, Sureo	Jaundice and chills during 2d month of period of exposure, nodular eruption, 40 days	

Average 35 yr, maximum 28 yr, minimum 30 days

TABLE 9—*Patients With a Past History of Carrion's Disease, With Blood Culture Negative for B Bacilliformis and Negative Agglutination Test*

Patient No	Duration of Residence in Endemic Region	Time Elapsed Since Termination of Disease	Type and Duration of Disease
1	21 days	126 days	Positive blood culture on 13th day of period of exposure subsequent cultures negative
13	5 mo	4 mo	Positive blood culture, 1 wk of evanescent eruption subsequent cultures negative
16	7 yr	5 yr	Subcutaneous nodules, 2 mo
18	3 yr beginning 8 yr prior to present data	6 yr	Extensive generalized eruption 6 mo
21	1 yr	58 days	Two subcutaneous nodules 15 days
24	15 yr	13 yr	Generalized eruption, 3 to 4 mo
26	2½ yr	2 yr	Large and small nodules, 2 mo
31	6 yr	6 yr	Three small nodules, short duration
34	?	14 yr	No details known
40	31 yr	18 mo	Moderately extensive eruption, 6 mo
44	4 yr	3 yr	Moderately extensive rash, limited to legs duration not known
46	7 yr	6 yr	Generalized eruption, duration not known
48	5 yr	Since 1st attack 12 yr Since 2d attack 5 yr Since 3d attack 1 yr	All three eruptions millary duration not exactly known, though each attack self limited
52	7 yr	11 yr	One nodule duration uncertain
53	8 yr	5 yr	Generalized millary eruption, duration uncertain
55	6 yr	6 yr	Minimal eruption, duration uncertain
56	2 mo 38 yr prior to present data, for 7 yr up to present	38 yr	Generalized and varied eruption for 1 yr
59	7 yr	5 yr	Minimal eruption, 6 mo
73	3 yr ending 5 yr prior to present data	Since 1st attack 8 yr Since 2d attack 7 yr Since 3d attack 5 yr	1st attack extensive varied eruption, 8 mo 2d attack similar to 1st, 4 mo 3d attack subcutaneous nodules
63	20 yr	11 mo	Millary eruption over extremities 2 mo
82	4 yr ending 8 yr prior to present data	10 yr	No details known
84	6 yr	Since 1st attack 5 yr Since 2d attack 4 yr	1st attack few subcutaneous nodules 2 mo 2d attack millary eruption, duration uncertain
86	1 yr	5 mo	Abundant millary eruption, duration uncertain
87	8 yr	7 yr	Varied millary and subcutaneous eruption, duration uncertain
88	3 yr ending 4 yr prior to present data and for 1 yr up to present data	6 yr	One subcutaneous nodule duration uncertain
89	10 yr	4 yr	Varied eruption, 4 mo
90	1 yr ending 6 yr prior to present data and for 1 yr up to present data	7 yr	Varied extensive generalized eruption, 1 yr
92	29 yr	6 yr	Millary and varied nodular eruption, 2 mo
102	15 yr	15 yr	Millary eruption on extremities, 1 mo
103	13 yr	5 yr	Millary eruption on trunk and leg, 1 mo
106	23 yr	Since 1st attack 18 yr Since 2d attack 15 yr Since 3d attack 13 yr Since 4th attack 3 yr Since 5th attack 4 mo	1st attack severe generalized eruption, 1½ mo 2d attack small nodules on legs and arms 3 mo 3d attack 4 to 5 subcutaneous nodules, 6 mo 4th attack millary eruption 1 mo 5th attack moderate number of nodules 6 mo
107	13 yr	12 yr	Two to three eruptions on face and legs, each 2 to 3 mo
108	7 yr	5 yr	Millary eruption, 8 mo
109	8 yr	3 yr	About 20 large nodules on both arms, 1 yr
123	2 yr	2 yr	Generalized millary eruption, 3 mo
124	28 yr	8 yr	Subcutaneous nodules, 15 days
125	2 yr	2 yr	Abundant varied eruption on legs and arms 2½ mo
126	1 yr	8 mo	Small scattered nodules, 4 mo
129	2 yr	9 mo	Extensive generalized eruption, 4 mo
143	29 yr	9 yr	Moderately severe millary eruption, 1 yr
144	36 yr	4 yr	Scattered nodules, 1 mo
147	20 yr ending 20 yr prior to present data	25 yr	Generalized millary eruption, 3 to 4 mo
151	6 yr	5 yr	Millary eruption, 3 mo
152	42 yr	24 yr	Varied generalized eruption, 1 mo
153	15 yr	15 yr	Millary eruption, 3 mo
154	1 mo 12 yr prior to present data and for 10 yr up to present data	12 yr	Generalized millary eruption 3 mo
156	16 yr	13 yr	Millary eruption on legs and arms, 6 mo
157	30 yr	29 yr	No details recalled
158	12 yr	10 yr	Millary eruption on face, arms and legs 3 mo
161	2 yr	2 yr	Minimal eruption 6 mo
170	5 yr	5 yr	Varied generalized eruption, 6 mo
171	41 yr	18 yr	Minimal generalized millary eruption, 2 to 3 mo
172	9 yr	7 yr	Two subcutaneous nodules 3 to 4 mo
173	12 yr	15 yr	Minimal millary eruption, 1 yr
178	18 yr	15 yr	?Evanescent millary eruption for 2 yr prior to present data
201	7 yr	1 yr	Minimal eruption, duration uncertain
Average	11 5 yr	5 9 yr	
Maximum	42 yr	38 yr	
Minimum	21 days	58 days	

TABLE 10—*Patients Resident in Endemic Regions With No Past History or Actual Evidence of Carrion's Disease, With Blood Culture Negative for B Bacilliformis and Negative Agglutination Test*

Patient No	Duration of Residence in Endemic Region	Patient No	Duration of Residence in Endemic Region	Patient No	Duration of Residence in Endemic Region
2	1 mo	83	18 yr	140	105 days
4	85 days	32	5 mo	142	1 mo
9	7 mo	85	22 yr	146	3 yr
25	33 yr	91	38 yr	148	50 yr
27	1 mo	94	6 yr	149	26 yr
28	2 yr	95	21 yr	150	27 yr
33	6 yr	99	1 yr	155	10 yr
41	13 mo	104	1 yr	159	7 mo
42	3 yr	105	20 yr	160	2 yr
43	30 yr	110	7 mo	163	4 mo
49	11 mo	112	6 mo	164	3 mo
50	5 mo	113	10 mo	165	3 mo
57	4 yr	115	32 yr	166	15 days
58	1 yr	116	30 yr	167	15 days
60	4½ yr	117	24 yr	169	8 yr
62	1 yr	119	14 yr	193	3 mo
67	36 yr	120	15 yr	199	4 mo
69	5 mo	130	105 days	202	10 mo
76	3 mo	133	114 days	203	43 days
79	1 yr	137	47 days	Maximum	50 yr
81	39 yr	139	105 days	Minimum	15 days

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Dr Marshall Hertig, head of the Department of Medical Entomology at the Institute, assisted in following up a number of patients. Dr José Jimenez Franco, of the Hospital Dos de Mayo, in Lima, assisted in gathering important clinical material. Dr Alberto Hurtado and the members of his service at the Hospital Arzobispo Loayza, in Lima, permitted access to several interesting cases. Dr Guillermo Ricketts Rey de Castro provided considerable data on patients in the Military Hospital of San Bartolome, in Lima. Dr Corrin Hodgson, of the British-American Hospital, in Lima, Dr Sergio E Bernales, Dr Carlos Protzel and Dr Pedro Roca, all of the Hospital Dos de Mayo, and Dr Victor Paltu gave me access to patients with Oroya fever under their care

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# COMPARATIVE VALUE OF DIGITALIS AND OF OUABAIN IN THE TREATMENT OF HEART FAILURE

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To the careful reader of the medical literature of the United States it is a matter of no small surprise to find so many articles dealing with the pharmacology and clinical applications of digitalis, as contrasted with the small number of papers published on the strophanthins and especially on ouabain

This same silence or oblivion is noted as one visits clinics and hospitals. Digitalis is not only the favorite but practically the sole drug employed in the treatment of heart failure,<sup>1</sup> whereas ouabain is looked on by specialists with disdain, and one might even add with distrust. Ouabain is generally considered to be imperfectly studied as regards its physiologic effects, uncertain in its clinical applications and dangerous in its results. At least, it is said that there is no reason for using ouabain when one has at hand such a sure agent as digitalis. This viewpoint was recently upheld by Gold,<sup>2</sup> who affirmed that there are no convincing proofs that intravenously administered strophanthin gives results which cannot otherwise be obtained by digitalis correctly handled.

This mental attitude toward ouabain is in frank disagreement with that held in European and Spanish-American countries, where the strophanthins, introduced into therapeutics by Fraenkel, and especially ouabain, recommended especially by Vaquez, are considered powerful weapons in the therapeutic arsenal against heart failure, for ouabain is as easy to manage and has been proved as safe as digitalis. It has its exact indications and its own field of application, and when limited to this field is capable of producing brilliant results, especially in those cases in which digitalis commonly gives poor ones or even fails completely.

A typical example of the European point of view is the following statement made by Vaquez:<sup>3</sup>

There is hardly another drug which rests on so solid a basis as does ouabain, a well defined chemical product of known toxicity, the pharmacodynamic actions of which have been studied by investigators of the greatest competence, of precise indications, administration and posology, all of which are the result of innumerable and concordant clinical observations. Arnaud's ouabain is the heroic remedy for acute or irreducible heart failure.

Similar statements have been made about strophanthin K (the product designated as strophanthin in the Pharmacopeia of the United States) by such authoritative

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1 Luten, D. The Clinical Use of Digitalis, Springfield, Ill., Charles C Thomas, Publisher, 1936.  
Levine, S. A. Clinical Heart Disease, Philadelphia, W. B. Saunders Company, 1936.  
Leaman, W. G., Jr. Management of the Cardiac Patient, Philadelphia, J. B. Lippincott Company, 1940.  
Fishberg, A. M. Heart Failure, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 721.

2 Gold, H. Recent Developments in Digitalis, Mod. Concepts Cardiovasc. Dis., 1942, vol. 12, no. 4.

3 Vaquez, H. L'ouabaine d'Arnaud, Arch. mal. du cœur 28:773, 1935.

German clinicians as Romberg,<sup>4</sup> of Munich, and Edens,<sup>5</sup> of Dusseldorf, and about ouabain by such eminent pharmacologists as Schmiedeberg<sup>6</sup> and Tiffeneau<sup>7</sup>

Such then are the two contrasting attitudes respecting ouabain, the one skeptical and the other enthusiastic. It is my belief that on scientific grounds there is no reason why such a discrepancy should continue to exist. A severe, critical study, both clinical and experimental, could rapidly and definitely confirm the excellence or the mediocrity of ouabain.

In Mexico and in the other Latin-American countries ouabain is employed regularly. I myself have used it extensively for the last twenty years, and in this paper I will try to summarize the impressions which as a clinician I have gathered from the use of it and to present in brief synopses, and by means of comparative charts, the different fields of application which I wish to review. The ouabain that I have employed has been prepared by Arnaud's method.

#### COMPARATIVE PHYSIOLOGIC ACTION

Digitalis and ouabain have similar physiologic actions. Both act fundamentally on the heart and only limitedly on the blood vessels. Both act partially through the vagus nerve and secondarily modify the circulation. But if the actions of the two are comparable, it does not follow that they are identical in every respect. Some physiologic mechanisms are more influenced by digitalis, while others are more influenced by ouabain.

Digitalis, as is well known, has a complex action on the myocardium. Certain functions are depressed, while others are stimulated. Digitalis depresses the activity of the auricular sinus, partly by direct action and partly by action of the vagus nerve, which results in a decrease in the number of heart beats, and it also depresses auriculoventricular conduction, which brings about a certain degree of blocking of the impulses descending from the auricle. On the other hand, it stimulates certain other functions of the heart. 1. It increases the irritability of the muscle fiber. 2. It increases its contractility, which is shown by the greater energy of the contraction. 3. It produces an increase in the general tone of the organ, which brings about a decrease in the size of the dilated heart.<sup>8</sup> From the influence of these combined actions there results, as Peters and Visscher<sup>9</sup> indicated, a greater efficiency in the work of the heart, which in turn gives, as Edens<sup>10</sup> pointed out, a better coronary blood supply.

Ouabain has these same physiologic actions but in varying degrees.<sup>11</sup> It depresses the automatism of the sinus and acts similarly on auriculoventricular conduction but to a lesser extent than digitalis. One frequently encounters a patient who has heart failure accompanied by tachycardia but who does not have

4 Romberg, E. *Tratado de las enfermedades del corazon y de los vasos*, Barcelona, Edit. Labor, 1931.

5 Edens, E. *A B C de la medication digitalique*, Paris, Pavet & Cie, 1938.

6 Schmiedeberg, cited by Romberg<sup>4</sup>.

7 Tiffeneau, M. *Étude pharmacologique et pharmacodynamique des glucosides strophan- tiques*, *Bull. d. sc. pharmacol.* **29** 68, 1922.

8 In speaking of the tone of the heart, I do not ignore the fact that agreement regarding its strict physiologic significance is far from being unanimous. However, to us clinicians the tone of the heart has an objective reality, and its failure is shown by a dilatation of the chambers, by reason of the deficit in the heart's ability to resist distention.

9 Peters, H. C., and Visscher, M. B. *The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It*, *Am. Heart J.* **11** 273, 1936.

10 Edens, E. *Die Digitalisbehandlung*, Berlin, Urban & Schwarzenberg, 1934, p. 446.

11 Hazard, R. *Les médicaments cardiovasculaires. L'ouabaine*, Paris, Centre de Documentation Universitaire, 1928.

arrhythmia (as may occur in hypertensive heart disease) and in whom under the influence of ouabain the cardiac failure is rapidly improved, but the tachycardia is not entirely corrected, rates higher than normal being maintained. It is also an equally common occurrence that in cases of fibrillation bradycardia produced by ouabain is much less accentuated than that resulting from the use of digitalis, which has a greater capacity for blocking the conduction system. It can, therefore, be stated that in those cases in which the action sought is depression of the conduction path, ouabain is decidedly inferior to digitalis in results obtained.

In contrast to its limited depressor action just mentioned, ouabain has a markedly stimulating effect on other functions of the myocardium, that is, the fundamental action of ouabain is expressed not in terms of the functions which it depresses but rather in terms of the myocardial functions which it stimulates. The contractility and the tone of the striated muscle fibers are considerably reenforced, which results in a distinct increase in the energy of systolic contraction and an appreciable reduction in the size of the heart. These two effects of ouabain represent the dominant characteristics of its action, and both are notably superior to those obtained with digitalis.

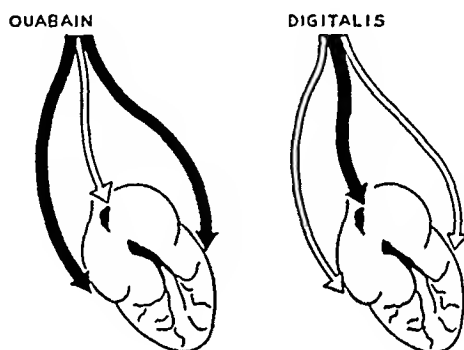


Fig 1—Graphic representation of the differences in the action of ouabain (stimulation of myocardial functions) and digitalis (depression of functions of the neuromuscular fibers)

Figure 1 permits one to appreciate these differences objectively. Compared with ouabain, digitalis has a predominant action on the excitoconductor system, this is to say, on the differentiated, or neuromuscular, fibers, the functions of which it depresses (chronotropism and conduction). Compared with digitalis, ouabain has a preponderant action on the striated, contractile fiber of the myocardium, the functions of which it stimulates (contractility and tonicity).

These facts stand out with equal clarity in figure 2, in which one can appreciate the pronounced increase in the amplitude of the ventricular contractions of a frog's heart, greater with ouabain than with digitalin, as well as the notably greater increase in tone when ouabain is given.

Figure 3 indicates the accentuated decrease in the size of a frog's heart when it is subjected to the action of ouabain, which is a reliable indication of a pronounced increase in tone. Digitalis does not ordinarily produce such wide variations.

Apart from their action on the heart itself, digitalis and ouabain have an inconstant effect on the arteries and the blood pressure. It is well known that though animals experimentally undergo an elevation in blood pressure, in human beings during periods of heart failure and under efficient but nontoxic dosage of these drugs no definite variations in blood pressure are noted. In some cases it remains unchanged, in others it is slightly diminished, and in still others there is a

moderate elevation of systolic pressure, combined or not with a lowering of diastolic pressure. It is generally accepted that in human beings nontoxic doses either of digitalis or of ouabain are not hypertensive and that when hypertension is observed it is always moderate, is cardiac and not arteriolar in origin and is restitutional in type, that is to say, it brings about a recuperation of the pressure rates, which had previously been lowered during the course of heart failure. And as far as the restoration of blood pressure is concerned, ouabain ordinarily produces greater elevations than digitalis, since it has a more intensive action on the contractile energy of the heart, as has just been mentioned.

Figure 4 outlines the commonly observed action of ouabain in the course of hypertensive heart failure.

There are, furthermore, two fundamental differences between digitalis and ouabain.

1 Digitalis and its glucosides are administered preferably by the oral route. Their absorption by way of the intestinal mucosa contributes toward their fixation

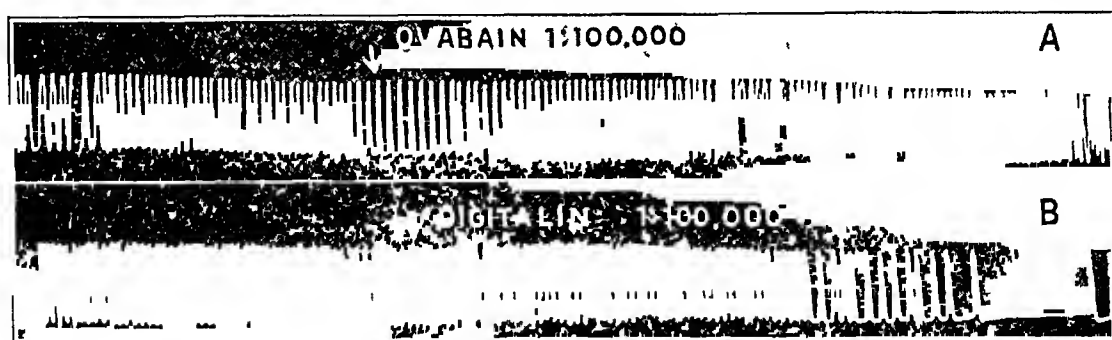


Fig 2—The effect of ouabain and digitalis on the amplitude of the ventricular contractions of a frog's heart. The isolated hearts of male frogs weighing 40 Gm (A) and 35 Gm (B) were employed.

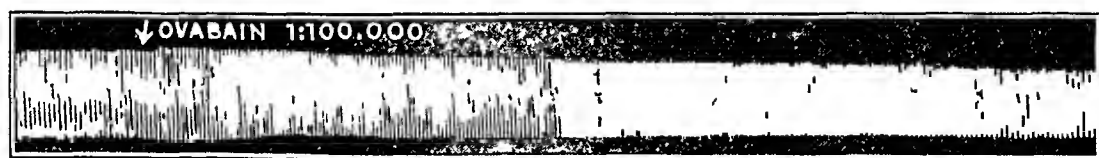


Fig 3—The accentuated decrease in the size of a frog's heart, a reliable indication of a pronounced increase in tone, when it is subjected to the action of ouabain. The isolated heart of a male frog weighing 35 Gm was employed.

on the heart at a slow rate. The action of digitalis begins to manifest itself one or two hours after administration, takes twenty-four hours to produce frank effects and requires forty-eight to seventy-two hours to reach its maximum.<sup>12</sup>

Ouabain, on the other hand, is largely hydrolyzed in the intestine, which renders uncertain its absorption by the oral route. On the contrary, its complete solubility in water permits one to inject it intravenously with ease. It requires only a few seconds to fix itself on the myocardium, its therapeutic action is observed before five minutes, reaches its greatest intensity in one hour and in twenty-four hours has disappeared.

2 Digitalis is an accumulative drug. In order to insure complete impregnation of the myocardium and to obtain a maximum effect, a dose six to ten times greater than the amount of digitalis destroyed in one day must be administered. When administration is discontinued the myocardium gradually uses

<sup>12</sup> Chavez, I. La digitalina, Tesis recepcional, Universidad Nacional, Mexico, 1920.



up the drug received, which prolongs its effect for six, eight and ten days after the last dose, on the condition, of course, that it was in reality a useful dose

Ouabain, on the contrary, does not accumulate. The dose at which the myocardium becomes saturated, that is, the one which affords the maximum effect, is the same as the dose destroyed in one day. When administration of the drug is discontinued its effects disappear in twenty-four to thirty-six hours. Only after a long series of injections (six to ten) can it barely be observed that the drug requires from forty-eight to seventy-two hours for its complete destruction.

In the other aspects of their use, digitalis and ouabain do not reveal any fundamental differences, except for those which vary in degree, by reason of their inherent characteristics. Consequently, they have the same generic action on heart failure, they produce the same changes on the ST segment and the T wave of the electrocardiogram, they have the same group of contraindications, and they produce identical signs of intoxication.

#### CLINICAL APPLICATIONS AND SELECTION OF THE SEPARATE FIELDS OF ACTION OF DIGITALIS AND OUABAIN

On keeping in mind the similarities and differences which have just been indicated, the separation between the two fields of action of digitalis and ouabain

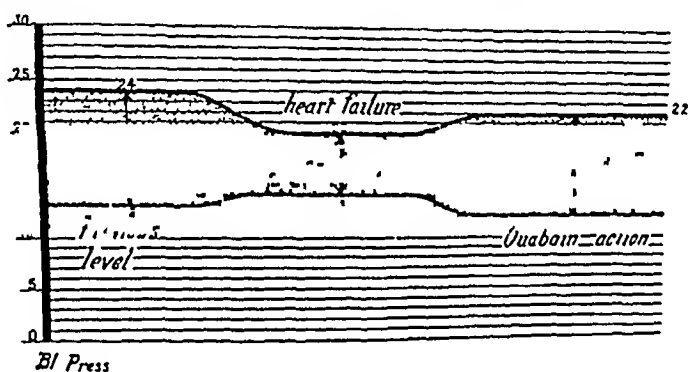


Fig 4—The action of ouabain in the course of hypertensive heart failure

seems quite logical. Let me express as comprehensively as possible the criteria which should guide one in the selection of cases.

1 Since ouabain has a rapid and intensive effect, its field comprises acute heart failure, or rather, the acute accidents of heart failure, paroxysmal nocturnal dyspnea, and attacks of acute pulmonary edema in persons suffering from failure of the left ventricle. However, not only do these advanced clinical pictures fit into its field of action, but their threatening stages as well, when it is legitimate to suppose that the effect of digitalis would not be exerted in time to dispel the danger.<sup>13</sup>

2 Since digitalis acts preponderantly by inhibiting the auricular sinus and by blocking the auriculoventricular bundle, its ideal field of action is in congestive heart failure, with pronounced tachycardia and particularly with auricular fibrillation. Usually, digitalis is ideal for use in rheumatic heart disease and chronic valvular lesions in young persons. In this field digitalis reigns supreme, and its results are spectacular.<sup>14</sup>

13 Vaquez, H. *Medicaments et medications cardiaques*, Paris, J. B. Bailliere et fils, 1925.  
Laubry, C. *Maladies du cœur et des vaisseaux*, Paris, Gaston Doin, 1930, vol. 3.

14 Stroud, W. D. *Diagnosis and Treatment of Cardiovascular Disease*, Philadelphia, F. A. Davis Company, 1940. White, P. D. *Heart Disease*, ed. 2 New York, The Macmillan Company, 1937.

3 Not only in acute heart failure, but in chronic failure of the left side of the heart as well, with or without congestive manifestations (fibrillation is usually lacking and tachycardia is moderate but enlargement of the heart, gallop rhythm, alternation of the pulse and a lowering of blood pressure are present), does ouabain assume first place. This is the common meeting ground for persons suffering from failure of the left side of the heart, chronic coronary insufficiency, long established hypertension and complicated syphilitic aortitis. Here it is that ouabain finds its greatest indications, strengthening systolic activity, diminishing diastolic dilatation, restitutionally increasing blood pressure and secondarily improving coronary circulation. This does not imply that digitalis is impotent to better this clinical picture, I only wish to affirm that its results are inferior when there is neither tachycardia nor fibrillation to be corrected, since it has less reinforcing action on the contractile fiber.

4 Once heart failure is under control, whatever its type, and when a prolonged sustaining treatment is to be maintained, digitalis is the drug of choice. The facility of determining the daily dose, the ease of oral administration and the sustained constancy of its effects make it quite superior to ouabain in prolonged treatments. The same can be said for prolonged sustaining treatments in cases of auricular fibrillation when the object is to hold down the ventricle to moderate rates. The supremacy held by digitalis here is indisputable.<sup>15</sup>

There still remain other more limited fields of application, of which some can be reserved for digitalis and others for ouabain. Suffice it for the purposes of this general view of the subject to summarize the four fundamental headings which have just been outlined by stating that digitalis is the ideal remedy in cases of congestive heart failure with tachycardia, specially with auricular fibrillation, in those cases in which fibrillation is a permanent feature but in which heart failure is not ostensibly present, and in unstable cases of heart failure in which prolonged sustaining cure is desired. Ouabain, on the other hand, is the heroic remedy for the acute phenomena of failure of the left ventricle, as it is also the remedy of choice for chronic failure of the left side of the heart in persons suffering from coronary arteriosclerosis, long established hypertension and aortitis.

In observing these fields more closely, one sees that the clinical pictures reserved for digitalis are those which commonly develop in children and in adults, in persons with chronic valvular disease and in patients with rheumatic heart disease more than in any others, that ouabain will be more frequently used for treating patients in the second half of life, aged persons and, above all, persons with vascular disease, coronary arteriosclerosis, hypertension, syphilis and cardiorenal disease.

The fact that digitalis when employed in the treatment of aged persons frequently gives poor results, at least ones not as satisfactory as those obtained in young persons, has already struck the attention of clinicians, and Willius<sup>16</sup> has recently enlarged on this view. The fact is certain, and the explanation is the one I have offered here. Heart failure in aged persons, commonly vascular in origin, responds much better to ouabain than to digitalis.

It is obvious, of course, that the fields of application of the two drugs are not always as clear as I have sketched them here. In children there are certain types of heart failure, with considerable cardiomegaly and moderate tachycardia, in which ouabain can better act on a greatly dilated, but rhythmic ventricle, and there are certain patients with coronary disease and failure of the right and the

15 Chavez, I. El campo de manejo de la digital, Arch latino am de cardiología y hematología 101, 1940.

16 Willius, F. A. El uso racional de la digital, Arch latino am de cardiología y hematología 5 33, 1935.

left side of the heart, largely congestive in nature, and with auricular fibrillation, to whom digitalis can be more useful. In other cases, the successive use of both drugs will be the rational treatment: first, ouabain, in order to correct the more striking accidents of heart failure, and later, digitalis, to control tachycardia and fibrillation. In this way, as Vaquez<sup>3</sup> and Edens<sup>5</sup> have pointed out, the initial administration of ouabain often has a reactivating effect which permits digitalis to render its maximum of efficiency.

#### TECHNIC OF THE ADMINISTRATION OF OUABAIN

I personally have used strophanthin K rarely. I have however, been using ouabain (prepared by Arnaud's method) extensively for the last twenty years, and all that has been said in this paper refers to it alone. Of it I can say that when correctly handled, I have never seen in thousands of patients treated one single death which could be attributed to it. It is known that the same cannot be said for strophanthin K.

But, as I have said, it is absolutely essential to handle ouabain correctly, and to that end it should be remembered that the margin of safety between the useful and the toxic dose is narrow, while with digitalis it is rather wide. Successful treatment depends on remaining within the vicinity of the useful dose, rather than approaching the limits of the toxic dose. More than 0.5 mg. of ouabain per day should be considered a toxic dose, such as those recommended by Danielopolu and those employed by Wyckoff and Goldring<sup>17</sup>. Easily toxic as well is such a daily dose if it is administered over a period of several days. Vaquez<sup>3</sup> recommended two injections of 0.25 mg. on the first day and a single injection on each of the two succeeding days, or a total of 1 mg. in three days.

As for myself, I have been accustomed to give a dose of 0.25 mg. per day for six days by the intravenous route exclusively. This series of six doses can be shortened if the patient begins to show signs of intolerance or can be lengthened to eight or ten, according to the benefit derived. Only exceptionally have I had to prescribe two doses on a single day of the series.

As a general rule, one series of injections of ouabain is sufficient to control overwhelming heart failure. Patients who suffer from long nights of insomnia and from the torment of dyspnea and crises of asthma, sleep like children once again after the first injection, or at most, after the second or the third one. Patients who have resisted digitalis rapidly recover under the action of ouabain. Its effect on nocturnal dyspnea in patients with cardiac disease is comparable only to that of morphine.

Once the series of injections of ouabain has been concluded, one can, if it is deemed necessary, continue treatment with digitalis. No interval of waiting is required, as ouabain is not a drug which tends to accumulate. On the other hand, when one wishes to change from digitalis to ouabain, it is imperative to wait a few days, according to the dose of digitalis administered.

Ouabain can be given for months and even years, when required, without variation in the dose needed or in the potency of its action. In an aged, overweight physician with coronary arteriosclerosis and massive heart failure in whom death seemed imminent and for whom therapy with digitalis had proved useless, I was able to sustain a cure with ouabain for two and a half years, with no greater

17 Wyckoff, J., and Goldring, W. Intravenous Injection of Ouabain in Man, *Arch. Int. Med.* **39**: 488 (April) 1927.

interruption then two days a week. During those two and a half years the patient was able to carry on a subnormal life and even found it possible to resume moderately the practice of his profession.

#### SUMMARY AND CONCLUSIONS

In the face of the divergence of opinion about the value of ouabain in the treatment of heart failure, the comparative actions of digitalis and of ouabain are outlined and the results of twenty years' experience in the use of ouabain are set forth.

Digitalis and ouabain have similar, but not identical, action on the decompensated heart. By way of comparison, digitalis exerts a more pronounced effect on the functions of sinus excitation and auriculoventricular conduction, which it depresses, ouabain, on the contrary, acts primarily on contractility and tonicity, which it stimulates.

Comparatively speaking, digitalis directs its chief effect on the differentiated, neuromuscular tissue of the heart, ouabain, on the undifferentiated, contractile fibers of the myocardium.

Digitalis, administered by the oral route, fixes itself slowly on the heart, ouabain, administered intravenously, acts with rapidity. The maximum effect of digitalis is reached in two or three days, whereas that of ouabain is reached in one or two hours. Digitalis accumulates, ouabain does not. On discontinuing the drug, digitalis extends its effects over a period of several days, up to eight or ten, those of ouabain disappear in twenty-four to thirty-six hours.

The best fields for the application of digitalis are congestive heart failure with tachycardia and specially with auricular fibrillation, fibrillation even in the absence of heart failure and long sustaining treatment of patients with slightly decompensated cardiac disease.

The best fields for the application of ouabain are the acute phenomena of failure of the left ventricle and chronic failure of the left side of the heart in patients with vascular disease, such as coronary arteriosclerosis, hypertension and syphilitic aortitis.

I recommend, as the best technic for the use of ouabain, one intravenous injection daily of 0.25 mg. in a series of six doses and more according to the tolerance of the individual patient and the clinical improvement obtained. In thousands of patients treated over a period of twenty years I have not encountered a single case of death attributable to ouabain.

# INVOLVEMENT OF THE LIVER IN DISEASE OF THE GALLBLADDER

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AND

SEYMOUR GRAY, M D

CHICAGO

Although the clinical demonstration of hepatic damage in cholecystic disease is of great importance in the medical and surgical management of disease of the biliary tract, there is little definite knowledge of this subject recorded in the literature. Studies of the incidence of hepatic involvement in disease of the gallbladder have not been conclusive and have not clarified the relationship between the two diseases. The purpose of this paper is to present new evidence of hepatic injury in disease of the gallbladder as detected by a simple laboratory method.

The presence of hepatic damage in disease of the gallbladder has been explained in three ways. One group of investigators<sup>1</sup> have stated the belief that the gallbladder is the primary source of infection and that the liver is involved by direct extension. Others have postulated that the liver acts as a bacterial filter of the body and is the chief source of the infection, involving the gallbladder secondarily by way of the bile ducts and lymphatics.<sup>2</sup> A third group of workers<sup>3</sup> have maintained that the pathologic changes in the liver and those in the gallbladder are completely independent of each other.

After Riedel<sup>4</sup> in 1888 first demonstrated enlargement of the right lobe of the liver in cholecystitis, no critical work appeared until 1918, when Graham<sup>5</sup> described the pathologic involvement of the liver in 30 patients with disease of the biliary tract. Biopsy specimens taken at operation showed microscopic evidence of inflammation of the liver in 87 per cent of the patients with acute and subacute cholecystitis. MacCarty and Jackson<sup>6</sup> studied the liver histologically in 58 patients with acute, subacute and chronic cholecystitis and demonstrated hepatic disease in 81 per cent. They could find no apparent relationship between the severity of the hepatic disease and the degree of inflammation of the gallbladder.

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From the Department of Medicine, the University of Chicago

1 Koster, H., Goldzieher, M. A., and Collens, W. S. The Relation of Hepatitis to Chronic Cholecystitis, *Surg, Gynec & Obst* **50** 595, 1930. Else, J. E., Rosenblatt, M. S., and Davis, A. M. The Relationship of Hepatitis to Cholecystitis, *Northwest Med* **29** 252, 1930.

2 Tietze, A., and Winkler, K. Die Beteiligung des Leberparenchyms an der Gallensteinkrankheit, *Arch f klin Chir* **129** 1, 1924. Genken, I. Pathologisch-anatomische Veranderungen in Leber und Gallenblase bei chronischer Cholecystitis ohne Steine, *ibid* **144** 752, 1927. Hadley, M. N. Liver Pathology and Physiology and Its Relation to Diseases of the Gall Bladder, *J Indiana M A* **20** 293, 1927.

3 (a) Martin, W. Hepatitis and Its Relation to Cholecystitis, *Ann Surg* **85** 535, 1927. (b) Noble, J. F. The Relation of Hepatitis to Cholecystitis, *Am J Path* **9** 473, 1933.

4 Riedel. Ueber den zungenformigen Fortsatz des rechten Leberlappens und seine pathognostische Bedeutung fur die Erkrankung der Gallenblase nebst Bemerkungen uber Gallensteinoperationen, *Berl klin Wchnschr* **25** 577, 1888.

5 Graham, E. A. Hepatitis. A Constant Accompaniment of Cholecystitis, *Surg, Gynec & Obst* **26** 521, 1918.

6 MacCarty, W. C., and Jackson, A. The Relation of Hepatitis to Cholecystitis, *Minnesota Med* **4** 377, 1921.

Judd in 1921 observed hepatitis at autopsy with infections of the gallbladder and biliary tract but never with peptic ulcer or appendicitis.<sup>7</sup> In 1924, however, Heyd, MacNeal and Killian,<sup>8</sup> investigating the incidence of hepatic disease in association with appendicitis and cholecystitis, found it as frequently with the former as with the latter. The degree of hepatic involvement was proportional to the chronicity of the infection. Mentzer<sup>9</sup> in 1926 made detailed postmortem studies of 548 patients with disease of the gallbladder. Sections for microscopic study were taken from the liver adjacent to the gallbladder and from the dome of the right and of the left lobe of the liver. The liver almost always showed hepatitis adjacent to the gallbladder, while sections taken from the left lobe were essentially normal even in patients with severe cholecystitis and cholelithiasis. Mentzer found that in 60 to 70 per cent of his patients there was pathologic evidence of hepatitis at postmortem examination regardless of the presence or absence of cholecystic disease. Noninflammatory lesions, including cholestasis of the gallbladder, were associated with hepatitis in 97 per cent.

Noble<sup>10</sup> studied the livers and gallbladders microscopically in 212 unselected autopsies. All but 5 of the subjects showed inflammatory cellular infiltration of the liver, although a large number had no evidence of disease of the gallbladder and none had clinical evidence of cholecystitis. Colp, Doubilet and Gerber<sup>10</sup> made an intensive study of the liver in patients with acute and chronic cholecystitis, using special stains and taking specimens for biopsy deep in the parenchyma of the right and left lobes of the liver. They concluded that the periportal cellular infiltration observed in disease of the biliary tract is not specific and that there is no evidence that hepatitis is associated with cholecystic disease in the absence of jaundice. They observed focal cellular degeneration in the presence of jaundice and attributed these changes to bile stasis rather than to a primary disease of the gallbladder.

Although the majority of writers feel that there is a direct relationship between cholecystitis and hepatitis and that long-standing cholecystic disease leads to progressive damage to the liver, the evidence cited indicates that there are conflicting opinions as to the significance of mild cellular changes in the liver and that microscopic studies alone may not demonstrate conclusively significant disease and abnormal function of the liver.

Because of the liver's multiplicity of function and large margin of reserve, the ideal laboratory test for its functional capacity is difficult to achieve. Tests of hepatic function in the past have not been sensitive enough to detect early involvement of the liver in cholecystic disease or have been too complicated to permit collection of a large series of cases. The bromsulphalein test, for example, cannot be evaluated in the presence of jaundice, and consequently its value in the study of disease of the gallbladder is limited. Of Cantarow's<sup>11</sup> series of 49 patients with acute cholecystitis, 41 had a normal serum bilirubin content and only

7 Judd, E. S. Relation of the Liver and Pancreas to Infection of the Gallbladder, *J. A. M. A.* **77** 197 (July 16) 1921. Judd, E. S., Nickel, A. C., and Wellbrock, W. L. A. The Association of the Liver in Disease of the Biliary Tract, *Surg., Gynec. & Obst.* **54**: 13, 1932.

8 Heyd, C. S., MacNeal, W. J., and Killian, J. A. Hepatitis, in Its Relation to Inflammatory Diseases of the Abdomen, *Am. J. Obst. & Gynec.* **7** 413, 1924.

9 Mentzer, S. H. A Clinical and Pathological Study of Cholecystitis and Cholelithiasis, *Surg., Gynec. & Obst.* **42** 782, 1926.

10 Colp, R., Doubilet, H., and Gerber, I. E. The Relation of Cholecystitis to Pathological Changes in the Liver, *Ann. Surg.* **102** 202, 1935.

11 Cantarow, A. Hepatic Function. I. Noncalculous and Calculous Cholecystitis, *Arch. Int. Med.* **54** 540 (Oct.) 1934, The Van Den Bergh Reaction and the Bromsulphalein Test in the Estimation of Hepatic Functional Impairment, *Am. J. M. Sc.* **184** 228 1932.

5, or 12.2 per cent, of these had an abnormal bromsulphalein retention. A similarly low incidence of hepatic involvement was found in 244 patients with chronic cholecystitis without gallstones and in 88 patients with calculous cholecystitis whose serum bilirubin determinations were normal. Abnormal bromsulphalein retention occurred in 32, or 13 per cent, of the first group and in 11, or 12.5 per cent, of the second.

Quick,<sup>12</sup> in his original application of the hippuric acid excretion test to human beings, performed the test on 6 patients with disease of the biliary tract and found the liver normal in 4. Kohlsteadt and Helmer<sup>13</sup> found an abnormally low excretion of hippuric acid in 11 of 21 patients. The patients with normal excretion of hippuric acid made an uneventful recovery after cholecystectomy, while those with impaired hepatic function had a turbulent postoperative course or died of hepatic insufficiency, according to the degree of damage to the liver. Pohle and Stewart,<sup>14</sup> using the cephalin-cholesterol flocculation test, found 3 mildly positive reactions in 30 patients with chronic cholecystitis with or without gallstones, while 8 of 11 patients with a stone in the common duct gave positive reactions. Recently Mateer and co-workers<sup>15</sup> found impaired hepatic function in over 50 per cent of 67 patients with proved cholelithiasis by use of the intravenous hippuric acid, the cephalin-cholesterol and the colloidal gold test.

The controversial evidence presented by pathologists and by investigators studying hepatic function in cholelithiasis led us to make a further study of the incidence of hepatic involvement in disease of the gallbladder.

#### METHODS AND RESULTS

The colloidal gold test of the serum for hepatic disease<sup>16</sup> seemed particularly suitable for this study because of its marked sensitivity and because it permits of a large number of studies. The reaction was found positive by one of us<sup>16</sup> in over 90 per cent of 96 patients with hepatic disease, and the unusual sensitivity of the test has been confirmed by Loew and Noth<sup>17</sup> and by Mateer and co-workers,<sup>15</sup> who found that the reaction was positive in 21 per cent more patients than the reaction to the cephalin-cholesterol flocculation test in a study of 124 patients with disease of the liver. In some instances the colloidal gold test has indicated hepatic disease which was not demonstrable by other laboratory methods but was later confirmed by autopsy, biopsy or the consequent clinical course of the patient. Sweet, Gray and Allen<sup>18</sup> found it most sensitive in detecting hepatic involvement in hepatolenticular degeneration. False positive reactions have occurred in less than 5 per cent of 400 normal control patients whom we have studied.

12 Quick, A. J. The Synthesis of Hippuric Acid. A New Test of Liver Function, *Am J M Sc* **185** 630, 1933.

13 Kohlsteadt, K. G., and Helmer, O. M. A Study of the Hippuric Acid Excretion as a Test of Hepatic Function, *Am J Digest Dis & Nutrition* **3** 459, 1936.

14 Pohle, F. J., and Stewart, J. K. The Cephalin-Cholesterol Flocculation Test as an Aid in the Diagnosis of Hepatic Disorders, *J Clin Investigation* **20** 241, 1941.

15 Mateer, J. G., Baltz, J. I., Marion, D. F., Hollands, R. A., and Yagle, E. M. A Comparative Evaluation of the Newer Liver Function Tests, *Am J Digest Dis & Nutrition* **9** 13, 1942.

16 Gray, S. J. The Colloidal Gold Reaction of Blood Serum in Diseases of the Liver, *Arch Int Med* **65** 524 (March) 1940.

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The test requires only 0.1 cc of blood serum and is not affected by abnormal concentrations of serum bilirubin or blood lipids. Serum from patients with hepatic disease when properly diluted flocculates the colloidal gold solution, giving a syphilitic curve similar to that obtained with syphilitic spinal fluid. We believe that the flocculation of the colloidal particles depends on qualitative changes within the globulin fractions of the blood.

The colloidal gold test was performed on 100 patients with disease of the gallbladder confirmed by roentgenogram or surgical intervention. Ninety-seven of these patients had gallstones proved by one or both of these methods. There were 92 women and 8 men, their ages varied between 20 and 70 years with an average of 43 years. A careful history was taken to determine the duration of the disease, the degree and duration of jaundice, previous episodes of jaundice and other symptoms and the presence of fever and chills. Special inquiry was made into such predisposing factors to disease of the liver as the use of drugs (cinchophen, arsenicals, etc.) and previous catarrhal jaundice, syphilis, alcoholism, vitamin deficiencies, etc.

The 100 patients with proved disease of the gallbladder were classified into four groups according, first, to the past or present history of jaundice (or an elevated serum bilirubin determination) and, secondly, to the clinical evidence of infection of the gallbladder, such as fever, chills or leukocytosis. These four distinct groups, comprised (1) patients having jaundice with infection, (2) those having jaundice without infection, (3) those having infection without jaundice and (4) those having quiescent disease of the gallbladder (no jaundice or infection). The term "infection" is used in the clinical sense, to denote a history of fever or chills at any time in the disease process or the presence of leukocytosis or fever. Care was taken to exclude patients with inadequate histories or insufficient hospital studies. The first two groups had stones in the common duct with jaundice and the last two groups had stones in the cystic duct or within the gallbladder. The fourth group, classified as having quiescent disease of the gallbladder, gave no history of previous jaundice or chills and fever. Determinations of the serum bilirubin were normal, and there was no fever or leukocytosis during an adequate period of study. Some of the patients complained of vague abdominal distress, while others were asymptomatic, and the discovery of gallstones on roentgen examination was an incidental finding in many instances.

A positive reaction to the colloidal gold test, indicating hepatic disease, was found in 46 of 100 patients with disease of the gallbladder (table 1). There were 51 patients who were jaundiced or presented clinical evidence of acute cholecystitis, i. e. fever and leukocytosis. Evidence of disease of the liver was found in 55 per cent of these patients. The incidence was highest in the patients with jaundice and infection. Ten of the 17 patients (58.8 per cent) in this group gave a positive reaction to the colloidal gold test. Jaundiced patients without clinical evidence of infection of the gallbladder showed a slightly lower incidence of damage to the liver. 10 of the 19 patients (52.5 per cent) giving a positive reaction to the colloidal gold test. Patients with acute cholecystitis (fever, chills and leukocytosis) and no jaundice revealed the same incidence of hepatic involvement as those with jaundice and no clinical evidence of infection. In this group 8 of the 15 patients (53.3 per cent) presented a positive reaction to the colloidal gold test.

The incidence of hepatic damage was definitely lower in the group of patients with quiescent disease of the gallbladder. Only 18 of the 49 patients (36.7 per cent) in this group had hepatic involvement as determined by the colloidal gold test, in contrast to over 50 per cent in the groups with jaundice or infection.



It is evident that jaundice or infection of the gallbladder or both are associated with disease of the liver in a large number of patients. Since the duration of the jaundice or infection and repeated exacerbations and recurrences of the disease over a period of years might be important factors in producing hepatic damage, we studied the incidence of disease of the liver in relation to the duration of these symptoms. Although a further subdivision of these studies results in a

TABLE 1—*Incidence of Positive Reactions to the Colloidal Gold Test in Patients with Disease of the Gallbladder*

	Number of Patients	Incidence of Positive Reactions to Colloidal Gold Test			
		No	%	No	%
A Jaundice with infection	17			10	58.8
1 Duration of symptoms					
(a) 1 to 7 days	8	3	37.5		
(b) 5 weeks	4	2	50.0		
(c) 2 or more months	5	5	100.0		
B Jaundice without infection	19			10	52.5
1 Duration of symptoms					
(a) 1 month	4	0			
(b) 1 to 5 years	11	7	63.0		
(c) 5 to 10 years	4	3	75.0		
C Infection without jaundice	15			8	53.3
1 Duration of symptoms					
(a) 1 week	3	1	33.3		
(b) 1 to 2 months	6	3	50.0		
(c) 1 to 3 years	6	4	66.6		
D Quiescent disease of gallbladder (no fever or jaundice)	49			18	36.7
1 Duration of symptoms					
(a) 6 months to 1 year	18	11	61.1		
(b) 2 to 5 years	16	4	25.0		
(c) 5 or more years	15	3	20.0		
Total patients studied	100			46	46.0

TABLE 2—*Bacterial Flora of the Gallbladder and Bile*

	Number of Patients	Incidence of Positive Reactions to Colloidal Gold Test	
		No	%
A Growth	14	7	50
B coli	5		
Pneumococcus of type III	1		
Str haemolyticus	2		
Str viridans	1		
Staph albus	1		
Ps pyocyanea	1		
B typhosus	1		
B welchii	1		
Diphtheroids	1		
B No bacterial growth	8	2	25

relatively small number of cases in each group, we feel that there is sufficient evidence to indicate that the duration of disease of the biliary tract is an important factor in producing hepatic damage.

The incidence of disease of the liver increased with the duration of the symptoms in the 17 patients with jaundice and infection of the gallbladder (table 1). Hepatic damage was demonstrable in 37.5 per cent of patients whose symptoms were of one week's duration or less, in 50 per cent of patients with symptoms of five weeks' duration and in 100 per cent of patients with jaundice and infection of more than two months' duration.

TABLE 3—*Symptomatology, Bacteriology and Pathology of Disease of the Gallbladder*

Patient	Symptoms	Duration	Bacterial Flora of Gallbladder and Bile	Pathologic Changes in Gallbladder	Pathologic Changes in Liver	Reaction to Colloidal Gold
1 A G	Recurrent chills, fever and jaundice	6 yr	B coli, pneumococcus of type III, Str haemolyticus	Extensive fibrous and round cell infiltration, chronic cholecystitis and cholelithiasis	Cholangitis and biliary cirrhosis (autopsy)	Strongly positive
2 B V	Recurrent chills, fever and jaundice with colic	10 yr	B coli, Pseudomonas pyocyanea, Str viridans	Round cell infiltration, erosions and hypertrophy, chronic cholecystitis and cholelithiasis	Periductal and intralobular round cell infiltration, early fibrosis, fatty infiltration	Strongly positive
3 R B	Chills, fever, jaundice, colic (mild diabetes mellitus and obesity)	10 days	B coli	Gangrenous cholecystitis, cholelithiasis	Marked fatty infiltration, mild lymphocytic infiltration, vacuolation of liver cells	Positive
4 S P	Recurrent colic chills and fever no history of jaundice	10 mo	No growth	Acute cholecystitis, edema and thickening of gallbladder wall, hemorrhages, round cell infiltration and denuded mucosa, cholelithiasis		Positive
5 A B	Recurrent colic no fever, chills or jaundice	6 mo	No growth	Thickened muscularis, round cell infiltration, cholelithiasis		Positive
6 T M	Recurrent colic fever, chills and jaundice	6 yr	Str haemolyticus, Staph aureus, Str viridans	Chronic cholecystitis and cholelithiasis, cicatricial stenosis of common duct	Biliary cirrhosis of liver	Strongly positive
7 B K	A Colic, chills, fever and jaundice	3 wk	B coli Str viridans	Minimal round cell infiltration, small erosions, fibrosis of walls of gallbladder cholelithiasis		Negative
	B Postoperative colic, jaundice and fever	5 wk	B coli	Choledocholithiasis, dilatation of common duct		Positive
8 C R	Pain in right upper quadrant no jaundice, fever or chills	10 yr	No growth	Minimal round cell infiltration and fibrosis, one stone in cystic duct of gallbladder		Negative
9 T S	Recurrent fever and chills	1 mo		Empyema of gallbladder and cholelithiasis		Positive
10 D S	Recurrent colic, jaundice, fever and chills	5 yr		Cholelithiasis, large stone in common duct, dilated common and cystic ducts	Nodules in liver suggesting biliary cholesterosis dilated hepatic ducts	Positive
11 A G	Recurrent colic no fever, chills or jaundice	4 mo		Cholelithiasis adenocarcinoma of gallbladder	Adenocarcinoma of liver adjacent to gallbladder	Positive
12 A M	Recurrent epigastric pain, no jaundice, fever or chills	5 mo	No growth	Adenocarcinoma of gallbladder, cholelithiasis round cell infiltration and fibrosis	No metastases to liver	Negative
13 C D	Vague abdominal distress, occasional pain in right upper quadrant	10 yr	No growth	Minimal cellular infiltration, small mucosal erosions cholelithiasis		Negative
14 A K	Vague abdominal distress	20 yr	No growth	Minimal round cell infiltration, fibrosis, cholelithiasis		Negative
15 L H	Recurrent colic, no jaundice or fever	9 mo	Str viridans	Marked round cell infiltration, hemorrhages, mucosal erosions, cholelithiasis		Positive

The same increase in the incidence of hepatic damage with time was noted in the 19 patients with jaundice but without clinical or laboratory evidence of infection of the gallbladder (table 1). The patients with intermittent jaundice of one month's duration without concomitant evidence of infection of the gallbladder revealed no incidence of hepatic damage, intermittent jaundice over a period of one to five years caused hepatic involvement in 63 per cent of the patients, while similar symptoms for five to ten years increased the incidence to 75 per cent.

Repeated exacerbations of acute cholecystitis without jaundice increased the incidence of hepatic disease from 33 per cent at the end of one week to 50 per cent at two months and 66.6 per cent at three years (table 1).

Although 36.7 per cent of the 49 patients with quiescent disease of the gallbladder had a positive reaction to the colloidal gold test, the highest incidence of hepatic involvement occurred in the patients with the shortest duration of symptoms. In contrast to the groups with jaundice or infection, these patients showed a decrease in the incidence of hepatic damage as the period of quiescent disease of the gallbladder increased. The reaction to the colloidal gold test was positive in 11 of the 18 patients (61.1 per cent) with a history of six to twelve months' duration but indicated hepatic disease in only 4 of the 16 patients (25 per cent) whose history was of two to five years' duration and in 3 of the 15 patients (20 per cent) whose history extended over five years.

There appears to be a correlation between the bacterial flora of the gallbladder, the pathologic changes in the gallbladder and the incidence of disease of the liver as detected by the colloidal gold test (table 2). The gallbladder and bile of 22 patients with disease of the gallbladder were cultured. Growth was obtained in 14 of 22 instances. This consisted of *Bacillus coli*, which was the most prevalent organism, *Pneumococcus* type III, *Streptococcus haemolyticus*, *Streptococcus viridans*, *Staphylococcus albus*, *Pseudomonas pyocyanea*, *Bacillus typhosus*, *Bacillus welchii* and diphtheroids.

The reaction to the colloidal gold test was positive in 7 of the 14 patients (50 per cent) whose cultures were positive, in contrast to 2 of the 8 patients (25 per cent) whose gallbladder or bile yielded no bacteria. It is interesting to observe that the more virulent pathogenic organisms were isolated from the 7 patients with a positive reaction to the colloidal gold test while such bacteria as *Str. viridans*, *Staph. albus* and diphtheroids were cultured from the biliary tracts of the 7 patients with no evidence of disease of the liver. Moreover, the pathologic changes in the gallbladder, both gross and microscopic, were more severe and extensive in the 7 patients with both a positive reaction to the colloidal gold test and virulent pathogenic organisms than in the 7 patients with a negative reaction to the colloidal gold test and less virulent bacteria (table 3).

#### COMMENT

The injurious effect on the liver of recurrent jaundice and infection of the gallbladder is readily demonstrable in table 1. Although the incidence of a positive reaction to the colloidal gold test was highest in the group of patients with both jaundice and infection (58.8 per cent), hepatic damage was equally prevalent in the patients with jaundice alone (52.5 per cent) or with infection of the gallbladder without jaundice (53.3 per cent). The danger of delaying surgical intervention too long is emphasized by the fact that the increase in the incidence of hepatic damage parallels the duration of the disease. Repeated insults to the liver from recurrent jaundice, infection of the gallbladder or both increased the incidence of disease of the liver to 75 per cent, 66.6 per cent and 100 per cent, respectively, as the duration of the disease was prolonged.

Jaundice and infection together appear to cause hepatic damage more rapidly than jaundice or infection alone, a pronounced increase in the incidence of hepatic disease occurring within a few weeks. Severe infection within the gallbladder likewise produces rapid hepatic damage, as seen in patient T S (table 3, patient 9), who complained of recurrent chills and fever of one month's duration. The reaction to the colloidal gold test was positive, and empyema of the gallbladder with gallstones was found at operation. Four similar instances of empyema of the gallbladder were observed. The patients all showed a positive reaction to the colloidal gold test.

The incidence of hepatic damage was considerably lower (36.7 per cent) in the 49 patients with gallstones and quiescent disease of the gallbladder without jaundice or clinical evidence of infection of the gallbladder. Although an infection of the gallbladder is always present in patients with gallstones, the process in patients without clinical evidence of infection is milder, and the pathologic changes are much less marked, than those observed in patients who manifest such evidence of infection (fever or leukocytosis) or jaundice. The highest incidence of disease of the liver (61.1 per cent) occurs during the more acute stages of the disease in these patients. The infection within the gallbladder then becomes quiescent and apparently mild, and as the period of inactivity increases the regenerative power of the liver is adequate to reduce the incidence of hepatic disease to about 20 per cent in the absence of any recurrent acute infection or jaundice.

The mild pathologic changes observed characteristically on microscopic examination of the gallbladders of patients with quiescent disease of the gallbladder of several years' duration were illustrated in 3 patients with vague abdominal distress and pain in the right upper quadrant of ten to twenty years' duration (table 3, patients 8, 13 and 14). Sterile cultures of the bile and gallbladder and negative reactions to the colloidal gold test were observed. At operation gallstones were found and the liver appeared normal.

Recurrent distress of the gallbladder of short duration without jaundice, fever or leukocytosis is associated with more acute changes within the gallbladder and a higher incidence of hepatic disease. An example of this was seen in patient L H (table 3, patient 15), who complained of recurrent mild colic of the gallbladder of nine months' duration. There was no evidence of jaundice, fever or leukocytosis. Gallstones were found at operation, and microscopic study of the gallbladder revealed an extensive round cell infiltration, hemorrhages and erosions. *St. viridans* was cultured from the bile, and the reaction to the colloidal gold test was positive.

Recurrent infection of the biliary tract and jaundice of sufficient duration may result in cirrhosis of the liver. This was observed in 3 patients (table 3, patients 1, 2 and 6) with gallstones and recurrent fever, chills and jaundice of six to ten years' duration. The reaction to the colloidal gold test was strongly positive in all 3 patients, and microscopic studies of the liver revealed an extensive biliary cirrhosis in 2 (patients 1 and 6) and an early fibrosis with fatty infiltration in the third (patient 2). Severe inflammatory changes were observed in the gallbladders of all 3. It is interesting to observe that *Str. haemolyticus* was cultured from the gallbladders of 2 of the 3 patients and *B. coli*, *Ps. pyocyanea* and *Str. viridans* from that of the third. Other organisms found were type III pneumococcus and *Staph. aureus*.

The rapidity with which hepatic damage may be produced was demonstrated in a patient with mild diabetes (table 3, patient 3) who had colic of the gallbladder with jaundice and fever for ten days. The reaction to the colloidal gold test was positive ten days after the onset of symptoms. Two months later the gallbladder was removed. The reaction to the colloidal gold test had been positive repeatedly

during these two months. Gangrenous cholecystitis was found at operation, and a biopsy of the liver revealed marked fatty infiltration, round cell infiltration and vacuolation of the liver cells.

Carcinoma of the gallbladder is another complication of gallstones to be considered in the management of disease of the gallbladder. Adenocarcinoma of the gallbladder was found in 2 patients (table 3, patients 11 and 12) with cholelithiasis, in 1 of whom (patient 11) the tumor had invaded the liver. The reaction to the colloidal gold test was positive in this patient and negative in the one in whom no metastases to the liver were observed (patient 12). One patient with cholesterosis of the liver (patient 10) also had a positive reaction to the colloidal gold test.

Ravdin,<sup>19</sup> Portis<sup>20</sup> and others have emphasized the importance of evaluating hepatic insufficiency in the management of patients with disease of the gallbladder. The newer and more sensitive methods of detecting early disease of the liver should prove an additional guide in the preoperative and postoperative care of patients with disease of the biliary tract.

#### SUMMARY AND CONCLUSIONS

The colloidal gold test of hepatic function was performed on 100 patients with proved disease of the gallbladder. A positive reaction, indicating hepatic disease, was found in 46 per cent.

The incidence of disease of the liver was highest in the patients with jaundice and infection (58.8 per cent) and lowest in the patients with quiescent disease of the gallbladder (36.7 per cent) who presented no history or evidence of fever or jaundice.

The incidence of disease of the liver increased with the duration of infection of the gallbladder or jaundice but decreased with time in the group with quiescent disease of the gallbladder.

A correlation was noted between the bacterial flora of the gallbladder, the pathologic changes in the gallbladder and the incidence of hepatic disease.

Cirrhosis of the liver was found in 3 and carcinoma of the gallbladder in 2 of the 100 patients studied.

The importance of detecting early hepatic damage in the management of disease of the gallbladder was discussed.

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20 Portis, S. A. Should We Operate on All Our Cases of Gallbladder Disease?, *Radiol. Rev. & Mississippi Valley M. J.* **60** 90, 1937, Symposium on Medical Management of Gall-Bladder Disease, *M. Clin. North America* **23** 1, 1939.

# INFLUENCE OF THIAMINE ON INDUCED HYPERTHYROIDISM

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A study of the effects of thiamine on hypermetabolism induced by administration of desiccated thyroid gland was suggested by several observations. We noted that the administration of desiccated thyroid to depressed psychotic patients was associated with tachycardia, restlessness and apprehension of a degree which necessitated discontinuance of medication. Other patients, however, who previously had been given thiamine hydrochloride, tolerated the administration of desiccated thyroid well. They were less apprehensive and agitated, although the increase in the metabolic rate and in the cardiac rate were as great as in the previous group of patients.

Administration of small doses of desiccated thyroid to patients with a low basal metabolic rate often is attended by rapid action of the heart and complaints of nervousness and digestive disturbances. An increase in the basal metabolic rate could be accomplished in such patients with fewer complaints if adequate amounts of thiamine were given prior to the administration of desiccated thyroid.

In studies of induced deficiency of thiamine<sup>1</sup> the basal metabolic rates were found to be lowered in an irregular manner after several months of restriction of thiamine, they were lowered rarely when the deprivation of thiamine was severe and of short duration but more frequently when the deprivation was moderate and prolonged. In some subjects anemia developed, and it was thought that this effect of thiamine deprivation might account for the low metabolic rate. However, in other subjects anemia did not develop during the period of thiamine restriction, and in these the metabolic rates were equally low. The ultimate cause of the decrease of the basal metabolic rate of every subject was deprivation of thiamine, but the mechanism through which the deficiency of thiamine operated to produce the low metabolic rate was not clear. In every case administration of thiamine was associated with a return of the basal metabolic rate to normal, but the time of recovery of individual subjects was variable, weeks or months, even with vigorous treatment with thiamine, were sometimes required. Recovery of the rate of metabolic exchange to normal indicated that this adverse effect of deprivation of thiamine on the organism was slowly reversible. It generally is believed that a high rate of metabolism is associated with a high requirement for

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thiamine and, conversely, a low rate of metabolism with a low requirement for thiamine. Regardless of the mechanism involved, the lowering of the basal metabolic rate in thiamine deficiency would be protective and spare the tissue stores of carboxylase. In a study not yet reported, a low basal metabolic rate was not observed among 4 subjects who received 0.7 mg of riboflavin per day (0.35 mg per thousand calories) for two hundred and sixty-nine days.

It may be assumed that the initial decrease of the metabolic rate in thiamine deficiency is produced by suppression of secretory activity of the thyroid gland or that the hormone of the thyroid is less effective in physiologic processes if there is a deficiency of thiamine. The latter consideration would have a particu-

TABLE 1—*Composition of Basal Diet\**

Food	State of Preparation	Menu 1, Gm	Menu 2, Gm	Menu 3, Gm
Bread	Special recipe	230	230	230
Butter	As purchased	45	45	45
Cream, 35 per cent	As purchased	75	75	75
Beef, lean	Roasted	100	100	75
Sucrose	As purchased	50	50	50
Cake	Special recipe	50	50	50
Potato, Irish	Roasted	75	75	100
Rice, polished, dry	Boiled	25	25	25
Flour	Plain white	10	10	10
Jelly	As purchased	20	20	20
Puffed rice	Commercial (unfortified)	15		
Carrots	Canned	75		
Lettuce	Fresh	30		
Pineapple	Canned	80	80	
Gelatin, 20 per cent solution	Special recipe	100		100
Tomato	Canned	75		
Apricots, dried, sulfured	Cooked	30		
Farina, dry	Cooked		15	15
Apple sauce	Cooked		100	100
Lemon julee	Fresh		20	20
Celery	Fresh		30	30
Corn	Canned		50	
Cottage cheese	Washed, skimmed		35	35
Beets	Canned			50
Composition of standard diet †				
Carbohydrate			327 Gm	
Protein			67 Gm	
Fat			75 Gm	
Calories			2,260	
Thiamine			0.43 to 0.48 mg	
			(0.21 mg per 1,000 calories)	

\* Each menu was repeated every third day. Vitamin supplements were given as described in the text.

† The content of carbohydrate, protein and fat was calculated from the data of Chatfield and Adams (Chatfield, C., and Adams, G. Proximate Composition of American Food Materials, no. 549, United States Department of Agriculture, June, 1940). The content of thiamine was determined by the thiochrome method of Hennessy.<sup>2</sup>

lar bearing if the thyroid hormone affects primarily the mobilization of materials for oxidation and other enzyme systems have the role of oxidation of the mobilized intermediary metabolites.

In the study herewith reported, the influence of any decrease of activity of the thyroid gland during the restriction of thiamine was obviated by administration of desiccated thyroid at a level somewhat higher than the normal requirement. Therefore, we were able to study the effectiveness of the thyroid hormone in maintaining the metabolic rate during deprivation of thiamine. Volunteer subjects were used.

#### METHODS OF STUDY

The subjects were studied in the nutrition division and were provided with an ample diet and supplements of 2 mg of thiamine hydrochloride, 2 mg of riboflavin, 4 mg of pyridoxine hydrochloride, 10 mg of calcium pantothenate, 40 mg of nicotinic acid amide, 160 mg of

ascorbic acid and 0.2 Gm of halibut liver oil fortified with irradiated ergosterol (providing 10,000 U S P units of vitamin A and 4,000 U S P units of vitamin D) per day for thirty days to assure a good nutritional status. During the period of preliminary observation the subjects were accustomed to procedures and routines and, especially tests of the basal metabolism. After the period of preliminary observation 2 women (subject 1, aged 47, 172 cm tall, subject 2, aged 25, 158 cm tall) were selected for further study. These did not have any signs of nutritional disease or physical defects and were able and willing to cooperate.

The diet, given in table 1, was constructed of foods which commonly appear on American tables and contained 0.22 mg of thiamine per thousand calories. This diet was used throughout the entire period of study. It was analyzed for content of thiamine by the thiochrome method of Hennessy<sup>2</sup>. The caloric intake was adjusted to the requirement of the subject by giving fractions or multiples of the standard servings of the basal diet. Thus the ratio of thiamine to calories was maintained nearly constant.

In the period of study (Oct 5, 1941 to June 1, 1942) the diet was supplemented per day with 4 mg of riboflavin, 8 mg of pyridoxine hydrochloride, 20 mg of calcium pantothenate, 80 mg of nicotinic acid amide, 160 mg of ascorbic acid, 0.4 Gm of halibut liver oil fortified with irradiated ergosterol (providing 20,000 U S P units of vitamin A and 8,000 U S P units of vitamin D), 0.25 Gm of choline chloride, 0.2 Gm of ferrous sulfate, 0.6 Gm of tribasic calcium phosphate and 5 minims (0.3 cc) of compound solution of iodine U S P. The diet was supplemented with thiamine hydrochloride only in the first two and last two periods of study, in the amounts indicated in tables 2 and 3. In the third period deprivation of thiamine represented, so far as could be judged, the only dietary restriction.

In the period of preliminary observation, at intervals during the period of restriction of thiamine and again during the subsequent periods of administration of thiamine, determinations of the basal metabolic rate, determinations of the calcium, phosphorus and proteins in the serum, determinations of the lipids in the plasma, electrocardiograms, and blood counts were made. The pyruvic acid,<sup>3</sup> lactic acid<sup>4</sup> and dextrose<sup>5</sup> in the blood were determined when the subject was at rest in bed and after administration of dextrose orally and intravenously. Both oral and intravenous tests for dextrose tolerance were performed with the subject in the postabsorptive state and at rest in bed. For the oral test 50 Gm of dextrose in 250 cc of solution was given and repeated thirty minutes later (Exton-Rose dextrose tolerance test<sup>6</sup>). Samples of blood were taken for analysis just before administration of the first dose of dextrose and again at thirty, sixty and ninety minutes after administration of this dose. The values at sixty and ninety minutes are the most significant. Data on the determinations at sixty minutes are contained in tables 2 and 3. For the intravenous test 0.4 Gm of dextrose (0.8 cc of a 50 per cent solution of dextrose) per kilogram of body weight was administered in three minutes. The concentrations of pyruvic acid, lactic acid and dextrose in the blood were determined before administration of dextrose and at thirty, sixty and one hundred and twenty minutes after injection. The values at thirty minutes are the most significant. The results of the intravenous test were comparable to those of the oral test and are not included in the presentation of data. Data on the pyruvic acid, lactic acid and dextrose in the blood after administration of dextrose, dextrose plus insulin and insulin alone are contained in table 4.

An exercise test was standardized for each subject. It consisted of a unit of work completed in exactly two minutes. Samples of blood for analysis of the content of pyruvic acid and lactic acid were taken just before exercise, the subject being at rest in bed and in the post-absorptive state, and at five, thirty and sixty minutes after conclusion of the exercise. The results are contained in table 5.

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TABLE 2—*Observations on Subject 1*

Duration of Period, Days	Diet			Excretion of Thiamine, Micrograms			Basal Blood Pressure, Mm Hg		Basal Metabolic Rate		Biochemical Status *				
	Carbohy- drate, Gm	Protein, Gm	Fat, Gm	Calories	Thi- amine, Micro grams	Thiamine Supplement, Micro grams	In 24 Hr	In 48 Hr	Body Weight, Kg	Basal Pulse Rate	Maxi- mum, per Cent	Min- imum, per Cent	Pyruvic Acid, Mg per 100 Cc	Lactic Acid, Mg per 100 Cc	Dextrose, Mg per 100 Cc
13	321	65	90	2,350	602	4,000	130	63.6	118	60	78	-13	1.3	8.6	154
Period of Administration of Thiamine															
13	318	65	87	2,315	482	4,000	463	63.0	114	76	91	+15	1.9	12.5	162
22	307	67	87	2,279	479	9,500		62.2	118	60	105	+23	1.8	16.1	185
Period of Restriction of Thiamine and Administration of Thyroid †															
15	319	68	86	2,322	497		80	62.0	110	64	88	+14			
32	331	67	85	2,357	458			62.0	120	80	87	+13	2.0	16.3	186
46	330	67	77	2,281	497			61.8	116	71	86	+17			
61	328	67	72	2,228	475		56	61.4	118	72	93	+17	2.7	18.7	180
74	326	66	71	2,207	449		27	60.9	112	70	90	- 6			
88	327	65	75	2,243	430			60.4	114	70	81	+12			
103	323	69	73	2,225	454			60.0	101	66	98	+7	2.4	19.6	158
117	323	65	75	2,227	439		7	61.2	114	72	86	+10	3.2	20.9	134
136	316	65	75	2,199	456		7	59.7	104	60	81	+12	3.7	26.5	162
Period of Administration of Thyroid † and Increasing Amounts of Thiamine															
17	326	66	77	2,261	455	300	26	156	58.6	106	62	+11	2.4	16.2	172
33	342	67	79	2,347	482	600	45	125	57.8	104	51	+8	2.3	15.9	187
47	283	55	70	1,982	422	900	272	266	57.1	122	70	+22	2.3	16.8	155
61	311	62	75	2,167	447	1,200	415	284	56.0	122	80	+19	1.8	10.4	176
81	314	65	76	2,200	453	19,000		59.0	126	82	93	+29	2.6	23.5	155
Period of Administration of Thiamine															
13	320	66	74	2,210	460	4,000		58.6	130	72	80	+11	1.6	12.5	163
26	340	70	70	2,270	466	4,000		59.0	128	75	71	+6	1.3	10.6	166

\* Sixty minutes after the first dose of dextrose given orally

† One milligram of thiamine hydrochloride given subcutaneously

‡ Sixteenth gram of desiccated thyroid per day

TABLE 3—*Observations on Subject 2*

Duration of Period, Days	Diet			Excretion of Thiamine, Micrograms			Basal Blood Pressure, Mm Hg		Basal Metabolic Rate		Biochemical Status *					
	Carbo hydrate, Gm	Protein, Gm	Fat, Gm	Thi amine, Micro grams	Thiamine Supplement, Micro grams	In 4 Hr After Test Dose †		Body Weight, Kg	Basal Pulse Rate	Maxi mum, per Cent	Mini mum, per Cent	Pyruvic Acid, Mg per 100 Cc	Lactic Acid, Mg per 100 Cc	Dextrose Mg per 100 Cc		
						In 24 Hr	In 4 Hr									
6	340	72	81	2,377	451	4,000	463	56.9	108	53	72	+ 8	+ 4	1.3	8.6	148
Period of Administration of Thiamine and Thyroid ‡																
6	320	66	81	2,273	448	4,000		57.0	118	66	110	+17	+12			
22	315	70	85	2,305	462	9,500	484	57.3	118	50	90	+22	+20	2.10	15.8	168
Period of Administration of Thyroid ‡, Restriction of Thiamine																
15	308	68	86	2,278	503		88	57.4	125	54	87	+16	+16			
32	312	67	84	2,272	499			57.5	124	50	90	+20	+20	2.12	16.4	152
46	324	67	73	2,221	490			57.2	130	58	102	+22	+18			
61	336	68	71	2,255	464		17	55.6	130	60	114	+20	+20	2.00	15.2	172
74	330	66	74	2,340	449			55.5	132	70	96	+11	+11			
88	333	66	74	2,262	423		23	56.0	116	54	80	+19	+18			
103	320	68	74	2,218	453			55.0	118	52	83	+27	+25			
117	326	64	75	2,235	450		13	54.0	124	53	73	+16	+14	2.30	20.6	157
136	337	60	79	2,335	473		7	54.6	128	50	89	+17	+16	3.50	28.4	167
Period of Administration of Thyroid ‡ and Increasing Amounts of Thiamine																
17	345	67	78	2,350	467	300	57	54.2	122	68	70	+15	+14	2.30	19.1	166
33	332	67	79	2,307	466	600	172	53.3	118	50	78	+22	+20	2.00	15.4	204
47	346	67	78	2,354	486	900	248	53.6	112	53	93	+34	+33	1.90	15.1	159
61	321	65	77	2,237	453	1,200	735	52.6	118	64	72	+33	+32	2.20	16.3	131
81	340	67	77	2,321	488	19,000		52.4	128	63	76	+34	+28	2.00	16.8	146
Period of Administration of Thiamine																
13	340	65	76	2,304	470	4,000		50.4	118	68	80	+ 2	0	1.60	13.4	146
26	320	68	75	2,227	465			53.0	122	74	78	0	— 5	1.30	10.2	152

\* Sixty minutes after the first dose of dextrose given orally

† One milligram of thiamine hydrochloride given subcutaneously

‡ Five tenths gram of desiccated thyroid per day

Physical and neurologic examinations were made not less frequently than once each month. The urine was analyzed periodically for content of thiamine by the method of Hennessy.<sup>2</sup> Determinations of the twenty-four hour excretion served as a check on the intake of thiamine. At the end of the period of restriction of thiamine 1 mg of thiamine hydrochloride was given subcutaneously and the excretion determined for the ensuing four hours, the subject being maintained in the postabsorptive state. The excretion of the test dose of thiamine indicated in some measure the stores of thiamine in the tissues. The value of the test dose procedure for estimation of these stores has been discussed in another paper,<sup>7</sup> and additional data were provided by a study, not yet reported, on the thiamine requirements of man. It suffices to state here that an excretion of 200 micrograms or more within four hours after administration of 1 mg of thiamine indicates satisfactory stores of thiamine and that an excretion of less than 100 micrograms indicates a considerable depletion of these stores.

Basal metabolic rates were determined with a specially constructed Benedict-Roth type apparatus. The rate was determined for two ten minute periods on the day of the test. The large capacity of the oxygen reservoir of the machine, an excursion of 1 cm of the drum representing 5037 cc of oxygen, made for accuracy in the determination of the slopes of the curves. For convenience of presentation the basal metabolic rates in terms of calories

TABLE 4—*A Comparison of the Concentrations of Pyruvic Acid, Lactic Acid and Dextrose in the Blood of Subject 1 After Administration of Dextrose, Dextrose and Insulin or Insulin Alone (Preliminary Period) with Those After Administration of Thyroid and Thiamine\**

Procedure (Administration)	Excretion of Thiamine in 4 Hrs After Test Dose, Micro grams	Basal Metabolic Rate on Day of Test, per Cent	Time of Analysis of Blood															
			Minutes After Administration of Insulin †										Minutes After Administration of Dextrose †					
			0	15	45	75	105	0	15	45	75	105	0	15	45	75	105	
			Pyruvic Acid, Mg per 100 Cc					Lactic Acid, Mg per 100 Cc					Dextrose, Mg per 100 Cc					
			0	30	60	90	0	30	60	90	0	30	60	90	0	30	60	90
			Before Administration of Thyroid															
Dextrose		—10		11	12	15	15		82	116	149	153		90	152	144	107	
Dextrose plus insulin	446	—9	11	13	18	19	23	95	68	102	148	186	99	105	82	89	95	
Insulin		—8	11	13	17	20	22	24	60	94	139	172	102	62	38	49	50	
After Administration of Thyroid																		
Dextrose		+21		11	18	25	29		63	142	226	274		98	140	178	118	
Dextrose plus insulin	457	+23	12	15	24	24	21	60	98	222	225	178	92	74	60	85	102	
Insulin		+25	15	19	27	28	28	70	154	266	342	335	89	61	41	44	47	

\* The intake of desiccated thyroid was 0.6 Gm per day, the intake of thiamine hydrochloride was 4.500 micrograms per day at the time of the test in both periods.

† Insulin was given intravenously, in the insulin-dextrose test 40 units of regular insulin was given fifteen minutes before the first dose of dextrose. Dextrose was given orally, 50 Gm at zero time and another 50 Gm thirty minutes later.

per square meter of body surface have been converted into percentage of normal by the standards of Boothby and Berkson (1935).<sup>8</sup>

The basal pulse rate for a period of two minutes and the basal blood pressure were determined before the subject arose each morning and were checked by a second observer.

Continuously throughout the period of administration of thyroid U S P, 0.6 Gm (10 grains) per day was given to subject 1 and 0.5 Gm (8 grains) to subject 2. The preparation was made up into uncoated tablets which contained 0.06 Gm of desiccated thyroid per tablet. The daily dose was divided into two equal portions, and one portion was administered after each of two of the meals of the day. Frequent examination of the feces revealed no undigested tablets. Diarrhea was never observed, and disturbance of gastrointestinal motility was not detected in periodic estimations of the motility rate by roentgen examination after a meal of barium sulfate. The conditions of the study were strictly maintained.

7 Mason, H. L., and Williams, R. D. The Urinary Excretion of Thiamine as an Index of the Nutritional Level. Assessment of the Value of a Test Dose, *J. Clin. Investigation* **21**: 247-255 (March) 1942.

8 Boothby, W. M., Berkson, J., and Dunn, H. L. Studies on the Energy of Metabolism of Normal Individuals. A Standard for Basal Metabolism, with a Nomogram for Clinical Application, *Am. J. Physiol.* **116**: 468-484 (July) 1936.

TABLE 5—Data on Pyruvic Acid and Lactic Acid in the Blood After Administration of Dextrose Orally and After Exercise Effects of Treatment with Thiamine Hydrochloride

Duration of Intake Level, Days	Intake of Thiamine, Micrograms	Excretion of Thiamine Micrograms		Response to Dextrose *										Response to Exercise †			
				In 4 Hr After Test Dose			Minimal Basal Rate, per Cent			Pyruvic Acid, Mg per 100 Cc			Lactic Acid, Mg per 100 Cc			Basal State	
		In 24 Hr	In 4 Hr After Test Dose							30 Min	60 Min	90 Min	Basal State	5 Min	30 Min	60 Min	90 Min
130†	450	7	56	+10	11	2.6	3.7	3.1	3.4	13.9	26.5	21.7	1.2	5.0	2.8	1.5	4.4
17	750	26	156	+11	10	1.7	2.4	2.4	3.8	7.6	16.2	18.2	1.3	4.2	2.9	2.1	4.7
16	1,050	45	125	+8	11	1.5	2.3	1.9	4.7	16.8	13.0	11.1	1.1	4.6	3.4	2.6	5.1
14	19,450			+29	19	1.9	2.1	2.1		16.0	21.3	1.0	1.0	4.7	3.8	2.9	5.0
130†	450	7	48	+17	11	2.9	3.5	3.1	3.7	16.0	28.4	27.9	1.0	3.3	2.3	1.6	3.8
17	750	57	130	+15	10	1.8	2.3	2.1	4.3	10.5	19.1	18.6	1.1	4.1	3.0	1.6	4.2
16	1,050	172	200	+22	11	1.5	2.0	2.0	4.7	7.0	15.4	17.0	1.0	4.5	3.2	1.8	4.9
14	19,450			+34		1.9	1.9	1.9		15.1	18.3	1.1	1.1	4.5	3.6	2.0	4.5
100	1,600	800	336	—2	10	1.2	1.4	1.2	6.4	7.3	9.5	8.5	1.1	3.9	2.6	1.5	5.4
100	1,600	805	355	—11	0.8	1.1	1.2	1.3	3.8	6.0	10.3	12.2	1.0	3.6	2.9	2.1	4.5

\* Fifty grams of dextrose was given at zero time and 50 Gm thirty minutes later

† The test was standardized for the individual subject one unit of work in exactly two minutes Samples of blood were taken at intervals after discontinuance of exercise

‡ End of the period of deprivation of thiamine

## OBSERVATIONS IN VARIOUS PERIODS OF THE STUDY

*Period of Administration of Thiamine (Preliminary Period)*—In this period the first of the series of periodic examinations was made. Data on the pyruvic acid, lactic acid and dextrose in the blood after administration of dextrose are contained in tables 2, 3 and 5. The data of this period are typical of those from studies of many other subjects, and therefore they serve as "normal" data for reference in subsequent determinations.

*Period of Administration of Desiccated Thyroid and Thiamine*—This period, of twenty-two days, began October 5 and ended October 26. Administration of the relatively large doses of desiccated thyroid was associated with an increase of the basal metabolic and the cardiac rate and some degree of hyperactivity, but there were no subjective symptoms which caused complaints. The concentrations of pyruvic acid and lactic acid in the blood were normal when the subject was at rest in bed. However, they were abnormally high after exercise and after administration of dextrose. Data on pyruvic acid and lactic acid are contained in tables 2, 3 and 4. Electrocardiographic abnormalities other than sinus tachycardia and arrhythmia were not observed. The basal metabolic rates at the end of the period were approximately +20 per cent.

*Period of Administration of Desiccated Thyroid and Restriction of Thiamine*—This period, of one hundred and thirty-six days, began Oct 27, 1941 and ended March 11, 1942. Discontinuance of the administration of thiamine hydrochloride was associated with anorexia, fatigue and nervousness for a few days, but readjustment occurred to the lower intake of thiamine, for complaints were not again voiced until about the seventieth day. Both subjects then complained of loss of appetite, fatigue, nervousness, numbness and tingling of the feet and legs and aching of the muscles of the calves. There was some decrease of ability to rise from the squatting position or to mount a chair. The achilles tendon and patellar reflexes were moderately hyperactive. Defects of the sensory nerve pathways were not observed. The cardiac rate was not rapid (70 to 90 beats per minute) when the subjects had been at rest in bed, but it was rapid (100 to 130 beats per minute) when there had been even moderate exertion. In thiamine deficiency, bradycardia during rest in bed and tachycardia after exertion have been regularly observed.<sup>1</sup> The blood pressure was somewhat affected, the diastolic pressure tended to fall more than the systolic. The heart sounds were fainter, and the pulse at the wrist was weaker than it had been at previous examinations. The chief features in the electrocardiograms were evidence of sinus tachycardia and arrhythmia with some decrease in the amplitude of all complexes. The basal metabolic rates were decreased irregularly at levels as low as -7 to +11 per cent.

After one hundred and thirty-six days of restriction of thiamine, anorexia, weakness and soreness of the muscles of the legs were outstanding complaints. Nausea was becoming more frequent, maintenance of intake of food and of activity required vigorous persuasion. Weakness of the muscles of the calves of the legs made it extremely difficult for subject 1 to rise from the squatting position or to mount a chair, and subject 2 could not rise from the squatting position. The achilles tendon and patellar reflexes of subject 1 had disappeared, and, while the right patellar reflex of subject 2 could be obtained, the left patellar and both achilles tendon reflexes were absent. Acuity of perception of stimuli, such as the touch of a cotton wisp, a pin prick and application of warm and cool tubes to the thighs and legs, did not appear impaired, although subject 1 occasionally responded inaccurately. A definite defect in the sense of position of joints or

of perception of vibrations of the tuning fork (128 vibrations per second) was not observed. The plantar reflexes (Babinski) were not obtained. In a study not yet reported severe neurologic defects were caused by isolated deficiency of thiamine.

The systolic blood pressure of subject 2 had increased and that of subject 1 decreased. The diastolic pressure was approximately 50 mm of mercury. The pulse had a slapping quality at the wrist which was out of proportion to the pulse pressure observed. The electrocardiogram of subject 1 revealed a sinus tachycardia, slurring of the QRS complex in leads II and III, a tendency to left axis deviation, inversion of the T wave in lead III and inversion of the P wave in lead III. The T wave of lead IV R was positive, in lead CR<sub>2</sub> the T wave was diphasic and the R wave diminished. The outstanding features of the electrocardiograms of subject 2 were sinus arrhythmia, slurring of the QRS complex in lead II and notching of the QRS complex in lead III. In lead III both the T wave and the P wave were diphasic. In lead IV R the T wave was positive, the Q wave small and the ST segment elevated. In lead CR<sub>2</sub> the T wave was positive.

The basal metabolic rate of each subject after one hundred and thirty-six days of restriction of thiamine and administration of desiccated thyroid was somewhat higher than it had been on the seventy-fourth day. The concentrations of pyruvic acid and lactic acid in the serum after administration of dextrose were considerably increased above the initial value, which indicated that the high values for pyruvic acid incident to a deficiency of thiamine were superimposed on already high values incident to the administration of desiccated thyroid.

The progressive nature of the neurologic defects and the other signs and symptoms of a deficiency of thiamine necessitated discontinuance of its restriction, and therefore thiamine was administered in increasing amounts beginning March 12, 1942.

*Period of Administration of Thyroid and of Increasing Amounts of Thiamine* — Beginning March 12, 1942, thiamine hydrochloride was provided in increasing amounts so that data might be obtained on the requirement for thiamine in conditions of induced hypermetabolism. The initial supplement of thiamine hydrochloride was 300 micrograms per day. The daily dose was increased by 300 micrograms approximately every two weeks. A satisfactory excretion of thiamine (more than 200 micrograms per twenty-four hours or more than 200 micrograms per four hours after administration of 1 mg of thiamine hydrochloride subcutaneously) was not obtained until the intake of thiamine hydrochloride was about 0.6 mg per thousand calories. This represents a somewhat higher minimal intake than was required by subjects with normal basal metabolic rates (0.45 mg per thousand calories). The minimal intake of 0.6 mg per thousand calories cannot be set with certainty because the subjects began the period of increasing intake of thiamine with depleted stores of thiamine and because the only objective criterion for adequacy of intake was excretion of thiamine, other criteria which we have used to assess the status of thiamine nutrition were not applicable in the state of induced hypermetabolism. These data might tentatively be interpreted, however, as evidence that the rate of metabolic exchange as well as the total exchange of energy or materials influences the requirement for thiamine.

When the larger doses of thiamine hydrochloride (more than 0.6 mg per thousand calories) were administered, the basal metabolic rate rose to levels of +21 to +28 per cent for subject 1 and of +28 to +34 per cent for subject 2. The levels of pyruvic acid and lactic acid in the blood after administration

of dextrose fell only slightly in this entire period, and after exercise these levels were even higher than during the period of deficiency of thiamine (table 5)

Treatment with small doses of thiamine produced numerous complaints of anorexia, weakness and nervousness. Although the intake of food was approximately the same as in previous periods, the subjects lost weight rapidly. Further loss of weight was prevented for subject 2 and a gain secured for subject 1 when the intake of thiamine hydrochloride was raised to about 195 mg per day. It is assumed that the sharp rise in the metabolic rate incident to administration of thiamine caused the complaints and loss of weight, an apparent paradoxical response to treatment.

Appetite and strength rapidly returned when the larger doses of thiamine were administered. Neurologic defects incident to deprivation of thiamine disappeared gradually from subject 2, but the achilles tendon reflexes of subject 1 were absent even after one hundred and twenty days of treatment.

*Period of Administration of Thiamine Without Administration of Desiccated Thyroid*—When thyroid medication was discontinued, the basal metabolic rates fell to normal levels within two weeks. Normal values for pyruvic acid and lactic acid in the blood after administration of dextrose were obtained, this fact indicating that the abnormal values encountered during the period of administration of desiccated thyroid and thiamine were caused by an increased rate of metabolism and not by a deficiency of thiamine.

#### COMMENT

The data in tables 2 and 3 on the basal metabolic rates indicate that these were initially increased by administration of desiccated thyroid. The rates, which decreased irregularly during deprivation of thiamine, rose to consistently high levels when thiamine hydrochloride was again provided, no other change having been made in the regimen. These data seem to indicate that the thyroid hormone is less effective for the maintenance of metabolic processes during thiamine deficiency. In drawing this conclusion we assumed, however, that (1) administration of desiccated thyroid at a level somewhat higher than the normal requirement for the thyroid hormone reduces the activity of the thyroid gland to a minimum, and, therefore, a further reduction of secretory activity of the thyroid gland is not caused by the deficiency of thiamine, and (2) absorption of desiccated thyroid gland is not impaired during deprivation of thiamine. Evidence for or against the validity of these assumptions was not obtained.

The data provide additional evidence that the function of the thyroid hormone is primarily to mobilize metabolites for oxidation by enzyme systems of the organism.

The values for pyruvic acid and lactic acid in the blood after administration of dextrose (contained in tables 2, 3 and 4) indicate that the levels of these substances in the blood, and presumably in the tissues, were elevated during hypermetabolic activity induced by administration of desiccated thyroid. Elevated levels of intermediary metabolites in the blood and tissues might in themselves serve to exert a mass action effect which would produce a metabolic rate higher than normal. Data on subjects 1 and 2 for the period of deprivation of thiamine indicate that the levels of these substances rose in the state of thiamine deficiency and that the abnormal levels were corrected slightly when thiamine was administered and in full only when administration of desiccated thyroid was discontinued.

The data contained in table 5 illustrate an apparently paradoxical response to treatment with thiamine. At the end of the period of deprivation of thiamine, high values for pyruvic acid and lactic acid were encountered after administration of dextrose. These metabolites decreased with administration of thiamine approximately to the levels encountered in the second period of study (period of administration of desiccated thyroid with adequate thiamine). This indicates a cure of the metabolic defect caused by a deficiency of thiamine, however, at the end of the period of deprivation of thiamine the levels of pyruvic acid and lactic acid after a standardized exercise test were approximately the same (in a few instances higher and in others lower) as those for normal control subjects. After administration of thiamine these levels after exercise became considerably higher. This apparent increase in the rate of mobilization of metabolites was associated with the increase in metabolic rate which followed administration of thiamine, the administration of desiccated thyroid was held constant.

#### SUMMARY AND CONCLUSIONS

Two physically healthy women, maintained continuously on a basal diet providing only 0.22 mg of thiamine per thousand calories but adequate in all other respects, received large doses of desiccated thyroid gland (subject 1, 0.6 Gm per day, subject 2, 0.5 Gm) for two hundred and forty-one days. Besides the periods of preliminary and subsequent observation the study was divided into three periods: Thiamine hydrochloride was liberally provided during the first period, of twenty-two days, it was restricted to 0.45 mg per day during the second period, of one hundred and thirty-six days, it was provided in increasing amounts during the third period, of eighty-one days.

The basal metabolic rate of each subject rose to approximately +25 per cent during the initial period of administration of thiamine and desiccated thyroid. It fell to -8 per cent and +11 per cent, respectively, during the period of restriction of thiamine, but rose to approximately +25 and +30 per cent respectively, in the third period, when thiamine hydrochloride was again provided.

Throughout the period of administration of desiccated thyroid the concentrations of pyruvic acid and lactic acid in the blood after administration of dextrose were high, but they were higher during the period of restriction of thiamine.

The conclusion appears justified that the thyroid hormone is less effective in promoting the metabolic activity of the organism in a state of thiamine deficiency. The results of this study may be interpreted as additional evidence that the function of the thyroid hormone is primarily to mobilize metabolites for oxidation by enzyme systems of the organism and only indirectly to increase the rate of oxidative processes.

The Mayo Clinic



# ELECTROCARDIOGRAPHIC CRITERIA OF LEFT VENTRICULAR HYPERTROPHY

FACTORS DETERMINING THE EVOLUTION OF THE ELECTROCARDIOGRAPHIC PATTERNS IN HYPERTROPHY AND BUNDLE BRANCH BLOCK

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Soon after the advent of clinical electrocardiography it was recognized by Einthoven and others that characteristic deviations occur in association with hypertrophy of the cardiac chambers. Important contributions were made by several early investigators,<sup>1</sup> but for a long time interest in electrocardiography was focused chiefly on differentiation of the arrhythmias and the diagnosis of myocardial disease, with little emphasis on the clinical value of the electrocardiogram as a means of detecting cardiac hypertrophy.

While the association of characteristic electrocardiographic patterns with hypertrophy of the various cardiac chambers is well recognized, the mechanism of these changes remains a subject of some controversy, and specific criteria for the electrocardiographic diagnosis of hypertrophy have not been established.

The present investigation was actuated by the necessity of establishing specific electrocardiographic criteria of left ventricular hypertrophy in connection with a study on prognosis of hypertension.<sup>2</sup> It was felt, and the belief was subsequently confirmed, that prognosis of hypertension was dependent not solely on the level of the blood pressure but on the duration of the hypertension, as evidenced by the degree of left ventricular enlargement. In order to classify subjects into

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From the Medical Department of the Equitable Life Assurance Society of the United States.

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2 Daley, R M., Ungerleider, H E., and Gubner, R S. Prognosis and Insurability of Hypertension with Particular Reference to the Electrocardiogram, *Proc A Life Insur M Dir America* **28** 18, 1941.

groups with and without electrocardiographic evidence of left ventricular hypertrophy, so that an actual mortality study could be made, it was first necessary to ascertain precisely what electrocardiographic abnormalities could be considered indicative of left ventricular hypertrophy

#### ELECTROCARDIOGRAPHIC CRITERIA OF LEFT VENTRICULAR HYPERTROPHY

It is generally appreciated that left axis deviation alone is of no significance as a sign of left ventricular hypertrophy, since it occurs in a large proportion of normal subjects. A study was therefore made to establish what electrocardiographic changes in association with left axis deviation could be considered indicative of hypertrophy.

The material for study comprised three groups of subjects: (1) 460 applicants for insurance with left axis deviation whose blood pressure was always below 140 systolic and 90 diastolic and for whom there was no record nor finding of any cardiac impairment, (2) 380 applicants with hypertension with left axis deviation whose blood pressure was always above 140 systolic and 90 diastolic, and

TABLE 1—*Voltage of the Ventricular Complex in Left Ventricular Hypertrophy*

Criterion	95%		99%		99.9%	
	Of "Normal" Subjects Are Below This Point	Which is Exceeded by This Percentage of Hypertrophy	Of "Normal" Subjects Are Below This Point	Which is Exceeded by This Percentage of Hypertrophy	Of "Normal" Subjects Are Below This Point	Which is Exceeded by This Percentage of Hypertrophy
$R_1$	13.9 mm	60.1	15.8 mm	42.6	18.1 mm	23.5
$R_1 + S_3$	22.1 mm	67.0	25.4 mm	51.9	29.1 mm	34.7
Higher of $R_1$ and $S_3$	14.0 mm	63.6	16.1 mm	45.7	18.4 mm	27.1
Higher of ( $R_1 + S_1$ ) and ( $R_1 + S_3$ )	15.6 mm	62.6	17.7 mm	46.0	20.2 mm	27.4
( $R_1 + S_3$ ) minus ( $S_1 + R_3$ )	19.2 mm	65.1	22.5 mm	50.0	26.1 mm	33.6

(3) 100 subjects with advanced hypertensive heart disease with left axis deviation in whom it may be assumed that left ventricular hypertrophy was present.

Group 1 was taken as normal, and group 3 represented hypertrophy. Group 2, consisting of applicants with hypertension, may be regarded as a mixed group in which a certain proportion of subjects had hypertrophy while the remainder were normal.

A study was made of the voltage of the QRS complex and of changes in the ST segment and the T wave. In the consideration of voltage two questions were investigated: 1. What combination of measurements of the R and the S wave in lead I and lead III is the most efficient criterion for the separation of persons with normal hearts from those with hypertrophy of the left ventricle? 2. With this criterion determined what is the dividing line between normal and abnormal hearts?

Five combinations of the R and the S wave in the standard limb leads were investigated: (1) the amplitude of  $R_1$ , (2) the sum of the amplitude of  $R_1$  and of  $S_3$ , (3) the higher wave of  $R_1$  and  $S_3$ , (4) the amplitude of the QRS complex in its taller lead, i. e., the sum of  $R_1$  and  $S_1$  or of  $R_3$  and  $S_3$ , and (5)  $(R_1 + S_3) - (S_1 + R_3)$ .<sup>12</sup>

The results are presented in table 1. It was found that criterion 2 is the most efficient, followed by 5 and then by 3 or 4 indifferently, while criterion 1 seemed poorest. Since the sum of  $R_1$  and  $S_3$  was found to be most valuable, consideration of voltage may be confined to this measurement.

Even with adequate data it is difficult to place an arbitrary dividing line as to just what sum of  $R_1$  and  $S_3$  should be considered abnormal. In 85 per cent of normal subjects with left axis deviation  $R_1 + S_3$  was less than 1.9 millivolts, in 90 per cent less than 2.0 millivolts, in 95 per cent under 2.2 millivolts, in 99 per cent under 2.5 millivolts and in 99.9 per cent less than 2.9 millivolts. On the other hand, these values were exceeded in a vastly greater percentage of subjects with left ventricular hypertrophy. Thus the sum of  $R_1$  and  $S_3$  exceeded 2.5 millivolts in only 1 per cent of normal subjects with left axis deviation, whereas this amplitude was exceeded by 52 per cent of subjects with left ventricular hypertrophy. It may therefore be regarded that when the amplitude of  $R_1 + S_3$  exceeds 2.5 millivolts hypertrophy is almost certainly present, when the sum exceeds 2.2 millivolts hypertrophy probably is present and that even a sum exceeding 2.0 millivolts suggests the likelihood of left ventricle hypertrophy.

High amplitude of the QRS complex not only occurs in the presence of marked hypertrophy but is an early change in left ventricular hypertrophy. This is indicated by the frequent occurrence of high amplitude among the intermediate group of 380 applicants for insurance notable only for elevated blood pressure, who may be considered as a mixed group composed largely of persons in the early stages of hypertension, as well as in small part persons in the later stages of the disease. It is of interest that 44.2 and 29.2 per cent of this mixed group fell above the 95 per cent (2.2 millivolts) and 99 per cent (2.5 millivolts) levels, respectively, of the normal curve.

Characteristic abnormalities in the terminal deflection of the ventricular complex, i. e., changes in the ST segment and the T wave, occur commonly in the presence of left ventricular hypertrophy. In the material studied these were not observed as frequently as increased amplitude of the QRS complex, and it appears that the changes in the ST segment and the T wave do not develop as early as increased voltage.

The changes in the ST segment and the T wave are less specific than increase in the amplitude of the QRS complex, since such changes occur in a great variety of conditions other than hypertrophy. It is generally stated that depression of the ST segment is significant if it is 1 mm or more (0.1 millivolt) below the isoelectric baseline.<sup>3</sup> However, analysis of the electrocardiograms of the 460 normal subjects with left axis deviation disclosed none with any noticeable depression of the ST segment in lead I, whereas this occurred frequently among the subjects with left ventricular hypertrophy. We, therefore, regard depression of the ST segment in lead I of any perceptible degree, i. e., as little as 0.5 mm, as suggestive of left ventricular hypertrophy in the presence of hypertension with left axis deviation. Caution must be exercised in interpreting the position of the ST segment when there is tachycardia or a prominent U wave. Flattening of the T wave to an amplitude of less than 1 mm or further degrees of abnormalities of the T wave in lead I likewise are to be considered suggestive of left ventricular hypertrophy when associated with left axis deviation in subjects with hypertension, since this was not observed among normal subjects. The depression of the ST segment and T wave negativity in lead I are accompanied by reciprocal elevation in lead III. As has been noted, while these changes are not specific for hypertrophy, nevertheless the pointed inversion of the T wave in lead I and the reciprocal relation of the terminal deflections in leads I and III are quite characteristic. In more advanced stages of left ventricular enlargement, as is well known, changes occur in the terminal deflections in lead II similar to, though less in degree than, those in lead I.

<sup>3</sup> Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed 4, New York, New York Heart Association, 1939.

Characteristic changes in serial precordial leads occur in association with left ventricular enlargement as described by Wilson<sup>4</sup>. These were not investigated in the present study, since serial precordial leads were not made. Lowering of the initial positive deflection in lead CF<sub>1</sub> was observed frequently in the presence of marked left ventricular enlargement. This may possibly be due to the fact that in marked left ventricular enlargement the precordial electrode in lead CF<sub>4</sub> bears about the same relation to the left border of the heart that normally exists in lead CF<sub>2</sub>, when the initial positive deflection is usually rather small.

The results of our study may be briefly summarized as follows. Left ventricular hypertrophy may be considered to be present when left axis deviation occurs in association with any of the following abnormalities in the ventricular complex:

1 Increase in the amplitude of the QRS complex, when the sum of the R wave in lead I and the S wave in lead III is over 2.5 millivolts. Hypertrophy is probably present if this sum exceeds 2.2 millivolts and is suggested when the sum exceeds 2.0 millivolts.

2 Depression of the ST segment in lead I of any perceptible degree, even as slight as 0.5 mm (0.05 millivolts).

3 Flattening of the T wave below 1 mm amplitude or further degrees of abnormality of the T wave in lead I.

TABLE 2—*Comparison of Electrocardiograms and Telcorontgenograms for One Hundred Subjects with Advanced Hypertensive Disease*

Electrocardiogram	Percentage of Subjects
Pattern of hypertrophy	66
Evidence of myocardial disease	11
Total abnormalities	77
Teleoroentgenogram	
Apex outside midclavicular line	52
Transverse diameter more than 10 per cent above that predicted	41
Cardiothoracic ratio above 50 per cent	36

#### COMPARISON OF ELECTROCARDIOGRAPHIC AND ROENTGEN CHANGES ASSOCIATED WITH HYPERTROPHY

Employing these criteria rather than the well known advanced pattern associated with marked left ventricular enlargement, a study was carried out to determine the relative value of the electrocardiogram in detecting left ventricular hypertrophy as compared with the roentgenogram. Analytic study was made of 100 subjects with advanced hypertensive heart disease, and the electrocardiographic and roentgen findings were compared. Three criteria were employed in estimating heart size in the teleoroentgenogram: the transverse diameter in relation to standards predicted from weight and height,<sup>5</sup> the relation of the apex to the left mid-clavicular line as seen in the roentgenogram and the cardiothoracic ratio. The results are presented in table 2.

It is evident, and this has not been sufficiently appreciated, that the electrocardiogram is valuable for detecting left ventricular hypertrophy and is more sensitive than the roentgenogram. This comparison is not intended, of course, to deprecate the importance of roentgen study, but it does emphasize the

<sup>4</sup> Wilson, F. N. Recent Progress in Electrocardiography and the Interpretation of Borderline Electrocardiograms, *Proc. A. Life Insur. M. Dir. America* **27**: 96, 1937.

<sup>5</sup> Ungerleider, H. E., and Clark, C. P. A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on the Teleoroentgenogram, *Proc. A. Life Insur. M. Dir. America* **25**: 84, 1938.

usefulness of electrocardiographic study in detecting early left ventricular hypertrophy. Electrocardiographic and roentgen changes do not necessarily parallel one another, and while electrocardiographic abnormalities occur relatively more frequently than roentgen changes, at times there may be definite evidence of left ventricular enlargement in the roentgenogram while the electrocardiogram is quite normal. Rounding of the left ventricular contour is suggestive of left ventricular hypertrophy even if the measurements are not perceptibly increased, as is often the case in the earlier stage of concentric hypertrophy.

#### MECHANISM OF ELECTROCARDIOGRAPHIC CHANGES

The findings of the present study, as well as of previous investigations on electrocardiographic changes associated with left ventricular hypertrophy, are the result of correlating empiric with clinical observations and, just as with most other aspects of clinical electrocardiography do not stem from theoretic considerations. Nevertheless, it is of great interest to consider the mechanism of the electrocardiographic changes associated with hypertrophy of the cardiac chambers.

#### AXIS DEVIATION

The association of an inverted QRS complex in lead III with left ventricular enlargement and an inverted QRS complex in lead I with right ventricular enlargement was noted by Einthoven and other investigators, and the terms left and right ventricular preponderance came into common usage as an expression of deviation of the electrical axis. While it has been well recognized for some time that axis deviation is determined by factors other than ventricular hypertrophy, the terms left and right ventricular preponderance continue to be widely and improperly employed as synonymous with left and right axis deviation.

Certainly it cannot be denied that the deviation of the electrical axis is influenced by cardiac enlargement and that left axis deviation is a usual concomitant of left ventricular hypertrophy. However, that left ventricular hypertrophy is the determining factor in producing left axis deviation even in normal subjects<sup>6</sup> appears untenable in view of the well known fact that left axis deviation is readily produced by transverse position of the heart without relation to heart size, by factors which elevate the diaphragm, such as expiration, pregnancy and ascites, or by body build. Indeed, there is strong reason to believe that in hypertension, which is the commonest cause of left ventricular hypertrophy, position of the heart plays a determining role in accounting for left axis deviation apart from the factor of hypertrophy itself. The occurrence of left axis deviation in association with hypertrophy has been attributed to clockwise rotation of the heart on its longitudinal axis.<sup>7</sup>

The body build of subjects with hypertension is most frequently the obese heavy set type, in which left axis deviation occurs normally because of a transverse position of the heart. This association is clearly shown by analysis of the occurrence of left axis deviation in relation to body build in 422 subjects with hypertension.

It is evident that among underweight subjects with hypertension, who constitute a minority, left axis deviation is less commonly encountered but increases in direct proportion to the degree of overweight. Left axis deviation was encountered in a total of 78 per cent of subjects with hypertension, and an identical figure,

6 Master, A. M. *The Electrocardiogram and X-Ray Configuration of the Heart*, Philadelphia, Lea & Febiger, 1939, pp. 15 and 30.

7 van Nieuwenhuizen, C. L. C., and Hartog, H. A. P. *The Electrocardiogram in Hypertension with Especial Reference to Lead IV*, *Am Heart J* **13** 308, 1937.

of 78 per cent, was found for another series of 100 subjects with advanced hypertensive heart disease. Other investigators have reported left axis deviation in a similar or slightly lower percentage of cases.

It is apparent, on the one hand, that left axis deviation is closely related to body build and, on the other, that left axis deviation is not a necessary and invariable accompaniment of left ventricular hypertrophy. One does not imply that left axis deviation is entirely unrelated to left ventricular hypertrophy, for there is no doubt that left ventricular hypertrophy of itself is capable of producing left axis deviation, while conversely right ventricular hypertrophy ensuing late in the course of hypertensive disease tends to nullify the electrical effects of left ventricular hypertrophy and may cause left axis deviation to disappear. It may be stated, however, that left axis deviation does not seem to be an essential part of the electrocardiographic pattern of left ventricular hypertrophy. Other characteristic features of the electrocardiographic pattern in left ventricular hypertrophy, in the terminal deflections of the ST segment and the T wave, may evolve prior to or even in the absence of left axis deviation, as has been noted by Kaplan and Katz<sup>8</sup> and Barnes.<sup>9</sup> It has been our experience that this is particularly apt to occur in subjects of normal or of slender build, more often in association with left ventricular hypertrophy due to aortic insufficiency, nephritic hypertension or malig-

TABLE 3—*Relation of Axis Deviation to Body Build in Four Hundred and Twenty-Two Applicants for Insurance with Hypertension*

Percentage Deviation from Average Weight	Number of Subjects	Subjects with Left Axis Deviation	
		Number	Percentage
—20 or less	1	1	
—20 to —11	9	3	33
—10 to —1	41	21	51
0 to +9	103	68	66
+10 to +19	147	123	84
+20 or over	121	114	94
	422	330	78

nant nephrosclerosis. While these changes in the terminal deflection do occur in the absence of left axis deviation, they appear to evolve much more readily when left axis deviation is present, and the electrocardiogram appears to be somewhat less sensitive in detecting hypertrophy in subjects of slender stature.

The degree of left axis deviation does not bear any constant relation to the degree of left ventricular hypertrophy. While extreme left axis deviation where the QRS is completely inverted in lead II, as well as in lead III, is usually an abnormal finding, it does not indicate left ventricular hypertrophy but may denote an abnormal conduction pattern due to myocardial disease.

#### VOLTAGE

Voltage in the electrocardiogram is determined by several factors: the mass of cardiac muscle, the relation between the excitation process in the two ventricles, the position of the heart determining the direction of potential, and conduction through the body tissues to the electrodes. The last factor probably accounts for high voltage in leads taken directly over the precordium and the relatively high voltage which may be observed in children, but it has no bearing on changes in voltage associated with hypertrophy. Position of the heart is not a significant

<sup>8</sup> Kaplan, L. G., and Katz, L. N. The Characteristic Electrocardiograms in Left Ventricular Strain With and Without Axis Deviation, *Am J M Sc* **201** 676, 1941.

<sup>9</sup> Barnes, A. R. (a) *Electrocardiographic Patterns*, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 77, (b) pp. 66-67.

factor in explaining the high voltage in left ventricular hypertrophy, for voltage in the limb leads could not be related to body build in the 460 normal subjects with left axis deviation. An altered relation between the time of development of the excitation process in the two ventricles is responsible for the high voltage in ventricular extrasystoles and in bundle branch block. This factor, however, can hardly explain the high voltage in left ventricular hypertrophy, since the excitation process is most often normal in left ventricular hypertrophy and the QRS complex is not appreciably widened until an advanced stage, when bundle branch block may supervene. It appears, therefore, that the increased voltage is to be ascribed directly to an increased mass of left ventricular musculature. It should be noted, however, that increased voltage, particularly of the R wave in lead I was observed by Robb and Robb<sup>10</sup> as an immediate consequence of acute left ventricular strain where hypertrophy could play no part.

It may be emphasized again that high voltage of the QRS complex is the earliest and most frequent electrocardiographic change associated with left ventricular hypertrophy. The study has indicated the limits of normal voltage in the presence of left axis deviation. It is generally stated that voltage is abnormal if the QRS in the tallest lead exceeds 20 millivolts<sup>11</sup>. Our study, however, indicates the necessity of judging voltage in association with axis deviation. In the absence of left axis deviation, high voltage is of no significance. Voltage as high as 25 or even 30 millivolts, most frequently in leads 2 and 3, may be observed normally when left axis deviation is not present, particularly in young slender subjects. In association with left axis deviation much lower amplitudes of the QRS complex are vastly more significant, as has been indicated.

#### ABNORMALITIES OF THE ST SEGMENT AND THE T WAVE

There has been much speculation concerning the cause of the changes in the ST segment and the T wave associated with ventricular hypertrophy, and several explanations have been suggested. These changes have been ascribed by some investigators to hypertrophy itself,<sup>12</sup> which is assumed to result in an altered relation between the electrical potential of the two ventricles. It has been suggested that the conduction pathway is impaired<sup>13</sup> or lengthened owing to enlargement of the left ventricle with delay in excitation of the left ventricular myocardium. The similarity of the electrocardiographic patterns in left ventricular hypertrophy with those of left bundle branch block is cited as support of the hypothesis that impaired conduction through the left bundle branch is responsible for the changes in hypertrophy<sup>14</sup>. If this were the mechanism, it might be expected that the width of the QRS complex, which measures the duration of the excitation process, would be similarly prolonged, as it is in bundle branch block. Actually, the QRS complex is usually of relatively normal duration, except in the more advanced stages of enlargement. Characteristic changes in the ST segment and the T wave are frequently observed with QRS complexes of normal width<sup>15</sup>. It is highly improb-

10 Robb, J. S., and Robb, R. C. Hypertension Electrocardiograms Experimentally Produced and Anatomically Explained. II. Left Ventricular Strain, *Am J M Sc* **203** 634, 1942.

11 Pardee, H. E. B. Clinical Aspects of the Electrocardiogram Including the Cardiac Arrhythmias, ed 4, New York, Paul B. Hoeber, Inc., 1941, p 48. Footnote 3.

12 Master, A. M. Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension. Their Prognostic Significance, *Am Heart J* **5** 291, 1930.

13 Katz, L. N. Electrocardiography, Philadelphia, Lea & Febiger, 1941, p 291.

14 Master,<sup>6</sup> p 108.

15 Rykert, H. E., and Hepburn, J. Electrocardiographic Abnormalities Characteristic of Certain Cases of Arterial Hypertension, *Am Heart J* **10** 942, 1935.

able that lengthening of the conduction pathway is responsible for the electrocardiographic changes, since advanced changes in the ST segment and the T wave may be observed when the ventricular cavity is not enlarged during the stage of concentric hypertrophy, while the terminal deflections may be quite normal when the left ventricle is markedly dilated and the conduction pathway presumably lengthened, as in cases of aortic insufficiency

Recently Robb and Robb<sup>10</sup> have attempted to relate the changes in the ST segment and the T wave to strain produced by stretching of the individual bundles of muscle, which they stated involves the superficial layers to the greatest degree

The left ventricle is enclosed by four muscle masses which give way in sequence the superficial sinospiral first, the superficial bulbospiral next, later the deep sinospiral, and in extremis the deep bulbospiral muscle

The characteristic depression of the ST segment in lead I with elevation in lead III is ascribed by these authors to involvement of the superficial bulbospiral muscle

Certain pathologic and physiologic considerations suggest, however, that the characteristic electrocardiographic changes result from ischemia of the inner layers of the left ventricle rather than from involvement of the superficial bundles of muscle. If the greatest strain were placed on the superficial layers of muscle in hypertrophy, one would expect to find the greatest degree of pathologic change in this region. While the portions of the superficial sinospiral and bulbospiral muscles which curve inward to form the papillary muscles are frequently involved, the outer layers of the left ventricular myocardium are usually relatively normal, whereas diffuse involvement is regularly observed in the deeper layers of the left ventricle, particularly the subendocardial region. This vulnerability of the subendocardial region has been emphasized by Buchner and associates<sup>16</sup> and has been noted by Friedberg and Horn<sup>17</sup> and by one of us (R. G.) in collaboration with Master, Dack and Jaffe in a study of 48 cases of fatal coronary insufficiency<sup>18</sup>

Depression of the ST segment and abnormalities of the T wave similar to those encountered in hypertrophy occur regularly in association with a great variety of clinical and experimental conditions which cause pathologic changes in the inner subendocardial layer of the left ventricle. Among these may be mentioned acute and chronic anemia, carbon monoxide poisoning, shock, overexertion, anoxemia and mechanical trauma to the endocardium. When a condition such as acute anemia or other strain occurs in a subject with early hypertrophy, a latent electrocardiographic pattern of left ventricular hypertrophy may be brought out, which suggests that similar mechanisms are operative in evoking the electrocardiographic changes

It has been suggested because of the similarity of the changes in the ST segment and the T wave associated with hypertrophy to those observed in myocardial ischemia in more acute states that the abnormalities of the ST segment and the T wave represent a chronic metabolic strain<sup>19</sup>. There are several factors which may contribute to produce a relative inadequacy of coronary supply in

16 Buchner, F., Weber, A., and Haager, B. *Koronarinfarkt und Koronarinsuffizienz in vergleichender elektrokardiographischer und morphologischer Untersuchung*, Leipzig, Georg Thieme, 1935

17 Friedberg, C. K., and Horn, H. *Acute Myocardial Infarction Not Due to Coronary Artery Occlusion*, *J. A. M. A.* **112** 1675 (April 29) 1939

18 Master, A. M., Gubner, R., Dack, S., and Jaffe, J. L. *Differentiation of Acute Coronary Insufficiency with Myocardial Infarction from Coronary Occlusion*, *Arch. Int. Med.* **67** 647 (March) 1941

19 Barnes, A. R., and Whitten, M. B. *Study of T Wave Negativity in Predominant Ventricular Strain*, *Am. Heart J.* **5** 14, 1929



**hypertrophy** While the increased aortic pressure tends to augment coronary flow, it does not do so in proportion to the greatly increased work performed by the left ventricle. The capillary count per square millimeter, which is the true measure of blood supply, is relatively decreased in hypertrophy, as has been shown by Weain.<sup>20</sup> Furthermore, increased thickness of the hypertrophied muscle cells makes difficult rapid diffusion of oxygen, nutrients and metabolites. In addition to these factors which tend to cause a relative inadequacy of coronary flow there is often added an absolute reduction in coronary flow due to associated coronary artery disease, particularly when hypertension is present. Changes in the ST segment and the T wave associated with hypertension have been ascribed directly to coronary artery sclerosis,<sup>21</sup> but these changes occur as well in the absence of any significant coronary artery disease in hypertension.<sup>15</sup> Aortic stenosis and insufficiency, which also are frequent causes of left ventricular hypertrophy, likewise operate to reduce the absolute coronary flow. Further evidence that the changes in the ST segment and the T wave are due to a metabolic strain is suggested by the fact that the changes are reversible. These abnormalities have been observed to diminish or disappear promptly in cases in which marked lowering of blood pressure has attended therapy of hypertension by various measures, such as sympathectomy<sup>9</sup> and administration of thiocyanates, renal extracts and tyrosinase.

While these factors give adequate reason to believe that a relative coronary insufficiency is responsible for the electrocardiographic changes in hypertension, there is yet one other factor which appears to be important particularly in explaining the localization of myocardial involvement in the deeper layers of the left ventricle. It is involvement of this region which produces the characteristic electrocardiographic changes.

Johnson and Di Palma<sup>22</sup> have recently shown that there is a marked gradient in intramyocardial pressure from the epicardium to the endocardium. While the intramural pressure of external layers of the left ventricle does not rise high during systole, the pressure in the deeper layers of the left ventricular musculature rises to very high levels during systole, far above the aortic pressure. There must, therefore, be a complete arrest of flow in the coronary vessels supplying the subendocardial region of the left ventricle during a portion of systole. In the outer layers of the left ventricle coronary flow is not arrested during systole because the intramyocardial pressure is not as high. The superficial layers may receive a relatively greater supply because of diversion of blood flow from the deeper layers, where systolic flow is impeded. The earlier observations of Anrep and Saalfeld<sup>23</sup> suggested a complete cessation of flow in systole. While more recent studies<sup>24</sup> have indicated that some degree of intramural systolic inflow does occur, yet this may be shunted to the outer layer in the manner suggested. In the right ventricle and in the auricles the intramyocardial pressure during systole is much lower than the pressure within the coronary artery, and so coronary flow is not impeded during systole in these chambers. It is thus evident that the

20 Weain, J. T. Morphological and Functional Alterations of the Coronary Circulation, *Bull. New York Acad. Med.* **17** 754, 1941.

21 Levine, S. A. *Clinical Heart Disease*, ed 2, Philadelphia, W. B. Saunders Company, 1940, p. 161.

22 Johnson, J. R., and Di Palma, J. R. Intramyocardial Pressure and Its Relation to Aortic Blood Pressure, *Am. J. Physiol.* **125** 234, 1939.

23 Anrep, G. V., and Saalfeld, E. V. The Effect of Cardiac Contraction upon the Coronary Flow, *J. Physiol.* **79** 317, 1933.

24 Gregg, D. E. Phasic Changes in Flow Through Different Coronary Branches, in *Blood, Heart and Circulation*, Publication 13, American Association for the Advancement of Science, 1940, p. 81.

efficiency of the coronary circulation is poorest in the subendocardial region of the left ventricle, since flow is cyclic rather than continuous. This region will be the one to suffer most from ischemia by any reduction in coronary flow or increased oxygen requirements of the myocardium. Pathologic confirmation of the relative inefficiency of the coronary circulation in the deeper layers of the left ventricle is afforded by the observations of Mallory, White and Salcedo-Salgar<sup>24</sup>. These investigators noted that subendocardial infarcts heal less rapidly than those in the center of the myocardium or beneath the epicardium and are poorly vascularized.

This factor explains the vulnerability of the subendocardial region of the left ventricle in hypertrophy and the predilection of myocardial disease for this region in a great variety of pathologic states, whereas involvement of the outer layers of the left ventricle, the right ventricle and the auricles is relatively infrequent. When intraventricular pressure in the right ventricle is markedly elevated, as in pulmonic hypertension secondary to mitral disease, coronary flow may be impeded during systole<sup>25</sup> with ischemia and damage to the subendocardial region of the right ventricle, producing the characteristic changes in the ST segment and the T wave in leads III and II.

In case of prolonged coronary insufficiency degeneration of cardiac muscle occurs, with replacement fibrosis. This is most marked in the subendocardial region of the left ventricle, where the metabolic strain is greatest. The fibrosis may involve the Purkinje network, which ramifies in the subendocardium, either directly or by impairing the vascular supply. This results in abnormal conduction, with the appearance of slurring, notching and widening of the QRS complex, eventually progressing to the pattern of left bundle branch block, which is frequently encountered in long-standing and advanced left ventricular enlargement. The widening of the QRS complex in hypertrophy is only in slight part attributable directly to increased thickness of the left ventricular myocardium. Oppenheimer and Rothschild<sup>26</sup> showed that in cases of bundle branch block there are widely disseminated areas of patchy sclerosis of the subendocardial region. To quote their classic study,

The pathologic changes, especially the sclerosis, predominate in the endocardial and subendocardial layer, that is, in the region of the so-called Purkinje network, as compared with the outer two thirds of the ventricular musculature.

Left bundle branch block is much more common than right bundle branch block because the subendocardial region of the left ventricle is predominantly involved in myocardial disease. The pattern of right bundle branch block may evolve by a similar mechanism in long-standing right ventricular enlargement secondary to mitral valvular disease, chronic cor pulmonale and certain types of congenital heart disease, such as pulmonic stenosis, which place a strain on the right ventricle.

#### TERMINOLOGY OF ELECTROCARDIOGRAPHIC CHANGES

A conspicuous lack of uniformity exists in the nomenclature employed to describe the electrocardiographic patterns associated with left ventricular hypertrophy. Various terms, such as left ventricular strain, left ventricular preponderance, hypertrophy and enlargement, are employed. It would seem desirable that

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24a Mallory, G. K., White, P. D., and Salcedo-Salgar, J. The Speed of Healing of Myocardial Infarction, *Am Heart J* **18** 647, 1939.

25 Visscher, M. B. The Restriction of the Coronary Flow as a General Factor in Heart Failure, *J A M A* **113** 987 (Sept 9) 1939.

26 Oppenheimer, B. S., and Rothschild, M. Electrocardiographic Changes with Myocardial Involvement, *J A M A* **69** 429 (Aug 11) 1917.

a more uniform terminology be adopted in describing and interpreting the electrocardiographic changes. Certain terms, such as left ventricular preponderance, are confusing, since this description is often used interchangeably with left axis deviation, which of itself, of course, is not indicative of left ventricular hypertrophy.

Based on the genesis of the electrocardiographic abnormalities suggested here the following terminology appears more specifically descriptive of the anatomic changes in the left ventricle.

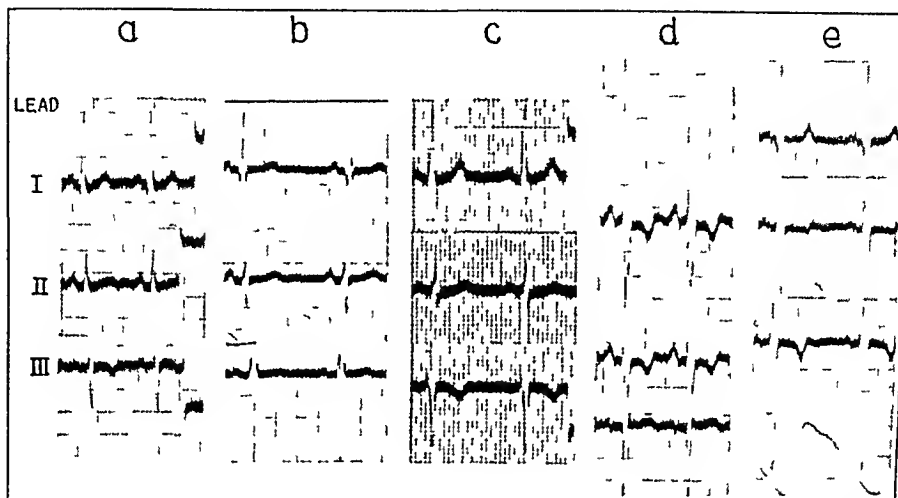


Fig 1—Left ventricular hypertrophy. Left axis deviation associated with high voltage of the QRS complex. (a) A high  $R_1$ , just exceeding normal limits. (b) A deep  $S_2$ . (c) The sum of  $R_1$  and  $S_2$  exceeds 2.5 millivolts. (d) An extremely high  $R_1$ . (e) An extremely deep  $S_2$ .

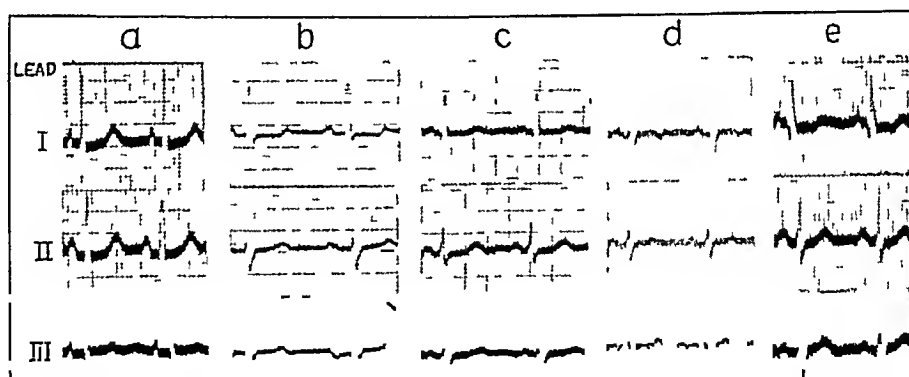


Fig 2—Left ventricular strain. Left axis deviation associated with changes in the ST segment and the T wave. (a) A slight depression of the ST segment in lead I. (b) A depression of the ST segment in lead I and a reciprocal elevation in lead III. (c) A low  $T_1$ . (d) An inverted  $T_1$ . (e) A depressed ST segment and a diphasic T wave in lead I.

*Left Ventricular Hypertrophy*—This term may be employed appropriately where left axis deviation is associated with increased amplitude of the QRS complex (the sum of  $R_1$  and  $S_2$  exceeds 2.5 millivolts or  $R_1$  or  $S_2$  individually exceeds 1.6 millivolts). The high voltage pattern is illustrated in figure 1.

*Left Ventricular Strain*—This term should be employed when characteristic changes are present in the ST segment and the T wave in the absence of high voltage (fig 2) or in the absence of left axis deviation (fig 3). The changes in

the ST segment and the T wave are less specific of hypertrophy than is high voltage. While characteristic changes in the terminal deflections are usually associated with left ventricular hypertrophy, similar abnormalities may occur in conditions other than hypertrophy when a metabolic strain is placed on the left ventricle (e.g., anemia). Well marked changes in the ST segment and the T wave may be present in the absence of high voltage of the QRS complex, and high voltage of the QRS complex may not infrequently disappear in the later stages of left ventricular hypertrophy with diffuse myocardial disease or after myocardial infarction.

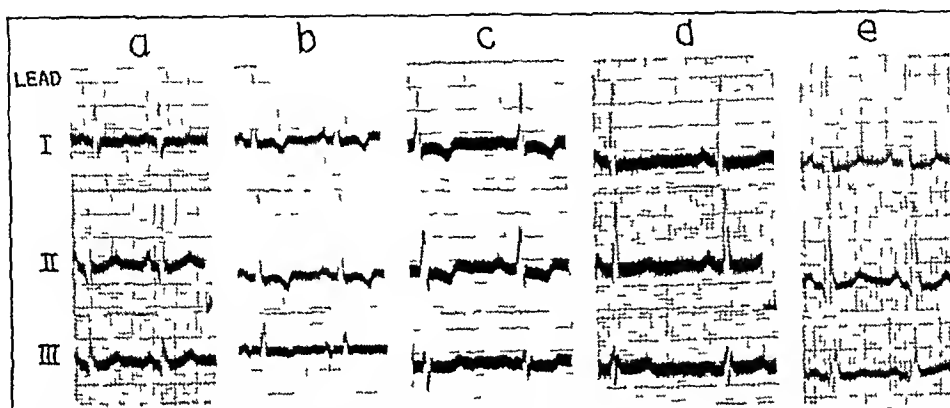


Fig 3—Left ventricular strain. Changes in the ST segment and the T wave in the absence of left axis deviation. (a) A diphasic T<sub>1</sub>. (b) Inverted T<sub>1</sub> and T<sub>2</sub>. (c) A depressed ST segment and an inverted T wave in lead I and lead II. There is a slight tendency to left axis deviation. (d) A tall R wave, a depressed ST segment and a diphasic T wave in lead I. (e) A tall R wave and a depressed ST segment in lead I.

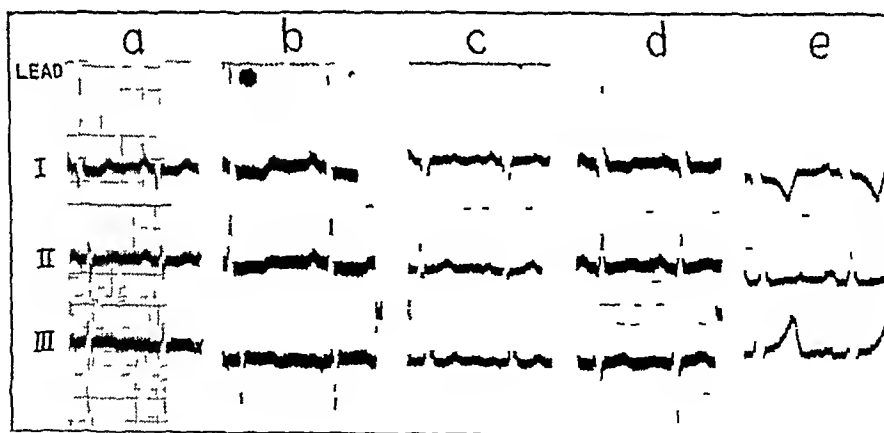


Fig 4—Left ventricular hypertrophy and strain. (a) A high voltage QRS complex, with the ST segment depressed in lead I and elevated in lead III. (b) A high R<sub>s</sub>, a depressed ST segment in lead I and lead II and an elevated ST segment in lead III. (c) A high voltage QRS complex and a diphasic T wave in lead I. (d) A high voltage QRS complex, a depressed ST segment and an inverted T wave in lead I. (e) A typical pattern, with a high voltage QRS complex and characteristic changes in the ST segment and the T wave.

*Left Ventricular Hypertrophy and Strain*—This term should be used to connote more advanced electrocardiographic changes when both the patterns of hypertrophy (high voltage of the QRS complex) and metabolic strain (changes in the ST segment and T wave) are present (fig 4).

*Left Ventricular Hypertrophy with Myocardial Strain and Fibrosis* (fig 5)—The final stage of left ventricular enlargement as revealed in the electrocardiogram includes, in addition to the aforementioned changes in QRS voltage and terminal deflections, abnormalities in the QRS complex, such as slurring, notching and

widening, progressing ultimately in its most advanced form to the pattern of left bundle branch block. These abnormalities in the QRS complex are considered to represent diffuse myocardial fibrosis ensuing after long-standing left ventricular strain, which involves the conduction system interfering with the excitation process.

The electrocardiographic patterns described do not always have an exact anatomic counterpart, for the pattern of left bundle branch block occasionally may be produced by localized involvement of the left main bundle branch in the interventricular septum without any necessary left ventricular disease otherwise. The pattern of left bundle branch block (fig 5 *e*) is encountered, too, in normal persons with a short PR interval, who are subject to attacks of paroxysmal tachycardia (Wolff-Parkinson-White syndrome). The pathogenesis of bundle branch block in such instances is not related to left ventricular enlargement or to myocardial disease but is believed to be due to aberrant conduction from the auricles to the ventricles.

While it may appear unwarranted to relate electrocardiographic patterns so specifically to the degree of anatomic change, a definite correlation between the severity of the electrocardiographic changes and prognosis has been demonstrated.<sup>2</sup> The criteria proposed indicate the precise electrocardiographic changes which may

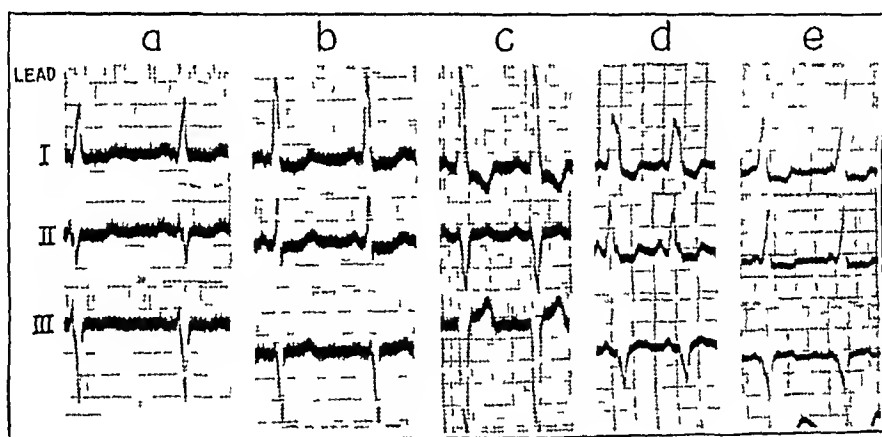


Fig 5—Left ventricular hypertrophy with myocardial strain and fibrosis. (a) A deep  $S_1$  and a depressed ST segment and a diphasic T wave in lead I. The QRS complex is slurred and notched. (b) A high voltage and depressed ST segment in lead I and lead II.  $R_1$  is notched. (c) Typical changes in voltage and terminal deflection. The QRS complex is widened to twelve hundredths of a second. (d) Left bundle branch block. The QRS complex is notched and widened to thirteen hundredths of a second. (e) Left bundle block with a short PR interval. This is not due to left ventricular hypertrophy but is an anomaly of conduction.

be considered diagnostic of hypertrophy, and the graded terminology of the more advanced changes further provides an approximate estimate of the degree of left ventricular enlargement, which is more graphic than any single phrase, such as left ventricular preponderance.

#### SUMMARY

An electrocardiographic diagnosis of left ventricular hypertrophy can be made before advanced changes have occurred. Employing criteria established by a study of a large number of normal subjects and persons with hypertension, we found that the electrocardiogram is a valuable device for detecting left ventricular hypertrophy and is somewhat more sensitive than the teleoroentgenogram. The electrocardiographic and roentgen changes do not necessarily parallel one another, and at times either may be relatively normal, while the other shows definite evidence of hypertrophy.

Left ventricular hypertrophy may be considered to be present when left axis deviation occurs in association with any of the following changes

1 Increase in amplitude of the QRS complex, best expressed by the sum of  $R_1$  and  $S_3$ . Hypertrophy is present if this sum exceeds 2.5 millivolts and is probably present if it is over 2.2 millivolts. The increase in voltage is the earliest electrocardiographic change in hypertrophy

2 Any perceptible depression of the ST segment in lead I, even of as slight degree as 0.5 mm (0.05 millivolt)

3 Lowering of  $T_1$  below 1 mm or further degrees of abnormality of  $T_1$

The changes in the ST segment and the T wave may develop in the absence of left axis deviation, and left axis deviation is not an invariable or necessarily integral part of the electrocardiographic pattern of left ventricular hypertrophy. It is shown that the usual occurrence of left axis deviation with left ventricular hypertrophy in hypertension is due largely to predominant obesity with transverse position of the heart, which in itself causes left axis deviation. In slender subjects with left ventricular hypertrophy left axis deviation is not so often observed.

The increased amplitude of the QRS complex may most reasonably be attributed directly to an increased mass of left ventricular musculature. The changes in the ST segment and the T wave are regarded as due to relative ischemia of the deeper layers of the left ventricle. This is occasioned by increased work of the heart without commensurate increase in coronary flow. Several factors, which are discussed, contribute to cause this disproportion.

The particular vulnerability of the subendocardial region of the left ventricle is due to an intramyocardial pressure gradient during contraction. During systole there is a marked increase in intramyocardial pressure in the deeper layers of the left ventricle, which exceeds aortic pressure and which obstructs coronary flow in this region, although there is no interference in coronary flow in the outer zone of the left ventricle or in the right ventricle or auricles, where the intramyocardial pressure does not rise above the arterial pressure. The subendocardial region of the septum and the left ventricle on this account is the area most vulnerable to ischemia. It is the site of predilection of myocardial disease when there is a relative insufficiency of coronary flow, as in hypertrophy, or when there is an absolute decrease in flow, as in coronary artery sclerosis and acute coronary artery occlusion.

Over a long period, the chronic subendocardial ischemia leads to irreversible changes and replacement fibrosis occurs. This involves the Purkinje distribution network of the left bundle branch which ramifies in the subendocardial region of the interventricular septum and the left ventricle. Interference with left ventricular excitation caused by diffuse involvement of the conduction system leads to slurring, notching and widening of the QRS complex, eventually progressing to the pattern of left bundle branch block, which is frequently encountered in association with long-standing and advanced left ventricular enlargement. The widening of the QRS complex is only in slight part attributable directly to increased thickness of the left ventricular myocardium.

Changes in the ST segment and the T wave in leads II and III, and ultimately right bundle branch block, occur in conditions associated with chronic right ventricular strain, such as pulmonic stenosis, cor pulmonale and long-standing mitral disease. The pathogenesis of these changes, just as in left ventricular hypertrophy, is similarly related to ischemia of the subendocardial region of the right ventricle consequent to increased intraventricular pressure in the right ventricle.

# THE QRS COMPLEX OF THE ELECTROCARDIOGRAM

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The electrocardiogram is a photographic record of the differences in electrical potential existing between two points on the body surface at every instant during the time the record is being taken. On the ordinates of the record one reads the potential differences, on the abscissas the time is given. When the electrocardiogram in the three standard limb leads is made, measurement of the potential differences at any instant in any two leads supplies data from which one may calculate the apparent direction and magnitude of the electromotive force at that instant as that force is projected on the frontal plane of the body. The direction of the force at each instant is the instantaneous electrical axis. Since the electromotive force has both direction and magnitude, it is a vector quantity. One may determine the magnitudes and directions of the vectors for each instant of the ventricular (or auricular) electrocardiogram and draw lines on paper representing them. If they are drawn in sequence so that they radiate from a common center, the distal ends of the vectors will describe a path which is known as the vectorcardiogram.<sup>1</sup> It is, indeed, possible to record this path directly by special apparatus.<sup>1</sup>

The use of vector analysis does not necessarily imply that the directions of the vectors are their true directions relative to the frontal plane. Such analysis is capable of extensive application and is useful, even though the directions as recorded are in error. Yet it has been widely assumed, if not by Einthoven, at least by many electrocardiographers, that the direction of the electrical axis is a true representation of the orientation of the electromotive force, relative to the frontal plane. The validity of this assumption has been denied by Katz,<sup>2</sup> by Wolferth, Livezey and Wood<sup>3</sup> and by others. Since we have tentatively accepted the validity of the Einthoven triangle hypothesis, at least as a close approximation, we cannot ignore the attack on it, and we shall return to it later.

The present paper deals with an attempt to explain the QRS complex in human beings in terms of successive stages of invasion of the ventricular muscle by the wave of excitation. Our method involves vector analysis. The value of this method has been greatly impaired by the difficulty of knowing the normal sequence of activation of the ventricular muscle. Although we may choose any instant during the course of that activation and calculate a vector representing the direction and magnitude of the electromotive force at that instant, we are unable to interpret the vector in terms of the particular region or regions of cardiac muscle which are becoming active at the chosen instant. If we await more precise, directly acquired knowledge of the sequence of ventricular activation in man, it is clear that we shall have to

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1 Wilson, F. N., and Johnston, F. D. The Vectorcardiogram, *Am Heart J* **16** 14, 1938

2 Katz, L. N. *Electrocardiography*, Philadelphia, Lea & Febiger, 1941, Concerning a New Concept of the Genesis of the Electrocardiogram, *Am Heart J* **13** 17, 1937

3 Wolferth, C. C., Livezey, M. M., and Wood, F. C. Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms, *Am J M Sc* **203** 641, 1942

wait indefinitely. For that reason we are compelled to take the electrocardiogram as it is recorded for a human being and to determine whether it is the picture which would necessarily be produced if the human ventricles are activated essentially in the same manner and sequence as the ventricles of the experimental animal. Fortunately, we now have access to reliable experimental observations, such as those of Lewis,<sup>4</sup> Eyster and Meek,<sup>5</sup> Harris<sup>6</sup> and also Nahum, Hoff and Kaufman,<sup>7</sup> which may be reinterpreted as necessary and applied to our problem. In certain details, for which experimental evidence on human beings is lacking, we have been compelled to infer the sequence of ventricular excitation from the electrocardiogram itself.

#### THE EXPERIMENTAL BASIS OF OUR PRIMARY ASSUMPTIONS

Every student of electrocardiography is familiar with the conclusions of Lewis and Rothschild<sup>8</sup> with respect to the sequence of activation of the ventricles in human beings. The wave of excitation is delivered simultaneously to the two ventricles by way of the branches of the atrioventricular bundle. Through a subendocardial Purkinje network, at a velocity of 3 to 5 meters per second, the impulses reach the ventricular muscle proper. The two sides of the septum were regarded as being first to be activated, the apical subendocardial muscle as activated later, the lateral ventricular walls still later and the bases of the ventricles last. From the subendocardial surfaces the activity was supposed to spread outward, at a rate of 0.4 meter per second, almost radially to the subepicardial muscle. Since the left ventricle is much thicker than the right one, the last part of the ventricles to be activated was supposed to be the subepicardial muscle at the base of the left ventricle. In spite of attempts to break down this relatively simple picture, it has met the demands of electrocardiography in human beings remarkably well, though we have found it necessary to modify certain details. Harris<sup>6</sup> in a recent excellent paper reported on the sequence of activation of the epicardial surface of the cat, dog and monkey ventricles, together with some observations on the subendocardial activation and the time required for the impulse to penetrate the ventricular walls in the dog. One may infer from his work that the time required by the impulse to activate the subendocardial surface is possibly shorter than the time assumed by Lewis and Rothschild<sup>8</sup>. Furthermore, the epicardial surface of the pulmonary conus is activated late, at least as late as the basal lateral wall of the left ventricle, and this probably holds for man. In the monkey, the apical and anterior surface of the right ventricle near the interventricular groove is earliest to be excited, the apical and anterolateral apical region of the left ventricle being activated only slightly later. In 1 monkey the latter region on the left was excited as early as the early region of the right ventricle—and we suspect that this individual difference also occurs in man. In the dog the impulse appears to pass from endocardium to epicardium roughly in a radial fashion, as postulated by Lewis, though it is possible that the pulmonary conus may be activated by impulses traveling longitudinally in muscle.

4 Lewis, T. *The Mechanism and Graphic Registration of the Heart Beat*, ed. 3, London Shaw & Sons, Ltd., 1925.

5 Eyster, J. A. E., and Meek, W. J. The Sequence of Fractionate Contraction at Different Surface Regions on the Right Auricle and Ventricles of the Dog's Heart, *Am. J. Physiol.* **134** 513, 1941.

6 Harris, A. S. The Spread of Excitation in Turtle, Dog, Cat and Monkey Ventricles *Am. J. Physiol.* **134** 319, 1941.

7 Nahum, L. H., Hoff, H. E., and Kaufman, W. (a) Formation of the R Complex of the Electrocardiogram, *Am. J. Physiol.* **134** 384, 1941, (b) The Nature of the S Complex of the Electrocardiogram, *ibid.* **136** 726, 1942.

8 Lewis, T., and Rothschild, M. A. The Excitatory Process in the Dog's Heart. The Ventricles, *Phil. Tr.* **206** 181, 1915.



bundles, as pictured by Robb and Robb<sup>9</sup> In the dog's left ventricle the time for impulse conduction from the endocardial to the epicardial surface is about 0.02 second In the right ventricle the time is much less The rather early activation of the epicardial surface of the anteroapical portion of the left ventricle may depend on Purkinje fiber pathways dipping into the wall, especially in the monkey Since man is also a primate, this may also be true of man Certain facts, particularly the behavior of the Q wave in right bundle branch block, have forced us to the conclusion that the subendocardial walls of the septum, especially on the right, are poorly supplied by connections between the Purkinje network and the myocardium proper Hence, although septal activation may start early in places, general activation of the septal surfaces may be later than activation of the subendocardial apical surfaces Similarly, the pulmonary conus, and possibly the basal rim of the left ventricle, may be poorly supplied by a subendocardial Purkinje network Because of the early activation of the subepicardial muscle adjoining the anteroapical part of the interventricular groove, we have assumed either that subendocardial activation is earlier in these regions or that it is earlier to involve the whole inner muscular surface We have carefully reviewed the valuable papers of Nahum and Hoff<sup>7</sup> and their co-workers On reinterpretation of their results in terms of acceptable fundamentals we find nothing incompatible with the assumption we have made, except that the orientations of the surfaces we have assumed for man differ from those reported by Hoff and Nahum for the dog Since they reported differences between the dog and the monkey, our assumption is not unlikely

The sequences of ventricular activation which we have chosen for man are shown in the figures and need not be stated at this point It is impossible here fully to recapitulate the fundamental postulates of electrocardiography, but a few points may be noted When a wave of excitation is moving through a ventricular wall, positive charges are present in front of the wave and negative charges at its rear The charges are close together The electrical vector produced is drawn pointing from the negative electrical field to the positive electrical field, i. e., in the direction in which the impulse is progressing The direction is accurately represented by having the vector point at right angles to the plane the margins of which are the boundary or edges of the polarized shell at the wave front of the excitation wave The length of the vector is proportional to the area of the opening in the polarized shell If two or more polarized shells are present, the combined magnitude and direction of these on the potentials of the limbs is the resultant effect of the two vectors, which is determined by application of the principle of the parallelogram of forces Figure 1 and its legend attempt to make the foregoing points clear The electrical fields are produced by the charges on the polarized shell, and the fields are distributed through the surrounding tissue, including both fully resting or polarized muscle or fully depolarized muscle Neither a fully active nor an inactive ventricular wall produces electrical effects or makes any contribution to the electrical fields In other words, each instantaneous electrical axis observed during inscription of the QRS complex is produced by the charges at the front of the depolarization wave and nowhere else<sup>10</sup> The electrical dipoles, each with its positive and negative charge, which are responsible for the T wave, are distributed through the muscle, unlike the dipoles responsible for the QRS complex This more difficult problem is not considered in the present paper The way in which these postulates are applied to the problem will be clear from the

9 Robb, J. S., and Robb, R. C. The Normal Heart. Anatomy and Physiology of the Structural Units, *Am Heart J* **23** 455, 1942

10 Craib, W. H. The Electrocardiogram, Medical Research Council, Special Report Series, no. 147, London, His Majesty's Stationery Office, 1930

figures and their descriptions. We assume that the reader is conversant with the method of determining the direction of an electrical axis by the Einthoven equilateral triangle method. In the preparation of the figures which illustrate the text, observations were made on human hearts in situ as exposed at autopsy, and clay models were constructed to facilitate visualization of the spatial relations of the ventricular walls.

It may be pointed out that although we believe the dipole theory of production of the waves of the QRS complex to be the correct one, nevertheless, if the reader prefers to visualize the active muscle as electrically negative and the inactive muscle as electrically positive, the consequences, so far as indirect leads are concerned, will be the same and the description given here will still apply.

#### SEQUENCE OF ACTIVATION OF HUMAN VENTRICULAR MUSCLE AND FORMATION OF THE QRS COMPLEX

Figures 2 through 7 illustrate the assumptions on which we have based our construction of the QRS complex in human beings. We may repeat that the

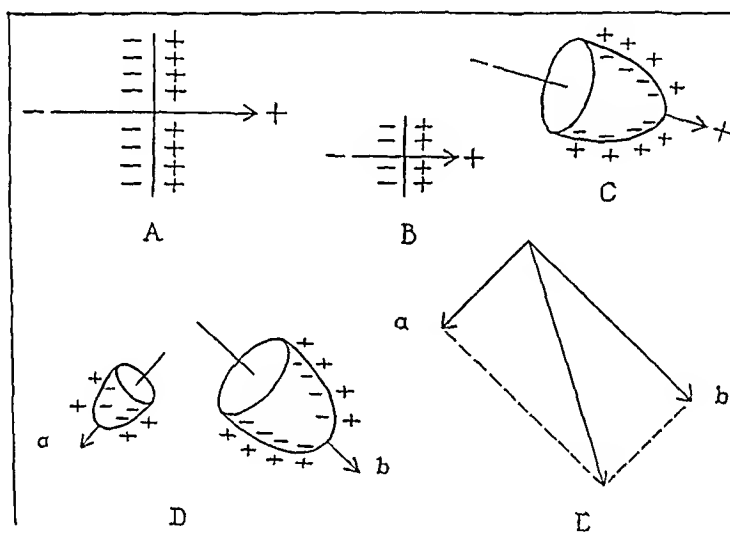


Fig 1—*A* and *B* show that the vector points from the negative side of the polarized membrane to the positive side and the length of the vector is proportional to the size of membrane (actual area), assuming the intensity of polarization is the same on the two. If the membrane is in muscle, the impulse is moving in the direction of the arrow. Current flow is from the positively charged side around through the external medium to the negatively charged side of the membrane. *C* shows that if the membrane, or shell, is curved like a cup, the vector points in at right angles to the plane of the opening in the cup and is proportional to the area of the opening. *D* shows two shells of unequal size. *E* illustrates the summation of the two vectors shown in *D* to produce the resultant vector.

sequence of activation as represented fits the facts of animal experimentation, but that experiment has not given all the facts needed. This is particularly true of activation of the interventricular septum.

The ventricles are shown as if rotated more on a longitudinal axis than is usual in the heart of a sthenic person. The direction of this rotation away from the average position is counterclockwise when the heart is viewed from the apex. This rotation, which is by no means uncommon for more transversely placed hearts, enables us to illustrate the regions being activated better than would be possible with a heart in the average position. The right ventricular wall is shown largely

cut away, there is a hole in the left ventricle above the apex, and another opening extends through the septum, so that its left ventricular surface can be represented in part, together with the right ventricular surface. The opening of the tricuspid valve appears as a dark oval. The valve leaflets, the papillary muscles and other detailed structures are not represented.

In figure 2 the impulse is shown to have invaded the right and the left surface of the septum, but it is assumed that the connections between the Purkinje system and the muscle are incomplete on the septal surfaces (Maham and Winston<sup>11</sup>)

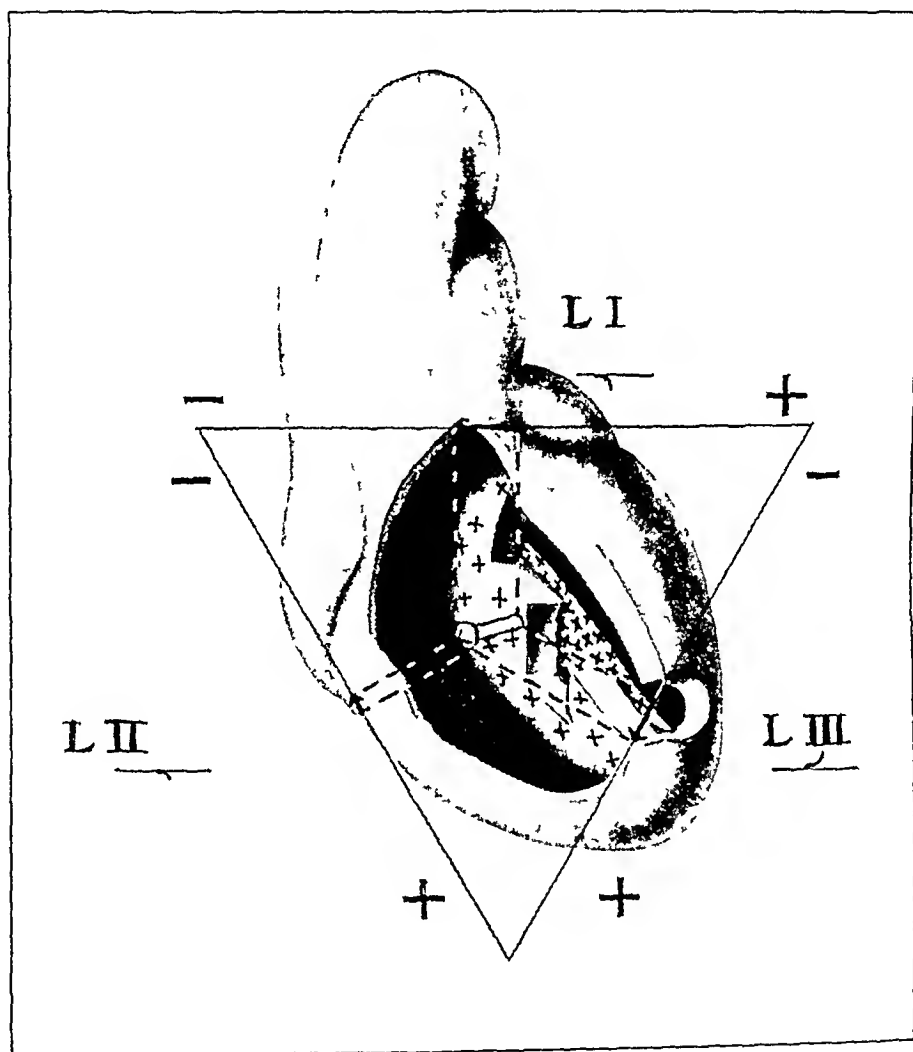


Fig. 2—The heart viewed from directly in front. The anterior wall of the right ventricle is cut away, together with most of the anterior margin of the septum, and an opening is shown above the septum and at the apex into the left ventricular cavity. Many crosses are shown on the exposed left surface of the septum and few on the right surface to indicate that activation is farther advanced on the left surface. The Q vector is represented by the white arrow "emerging" from the septal wall.

Hence, the surfaces are represented not as being fully active but as active only at certain points. The number of points of activation on the left surface is shown to exceed the number on the right surface. In consequence, depolarization is

<sup>11</sup> Maham, E. and Winston, M. R. Researches on the Comparative Anatomy and the Experimental Pathology of the Superior Connections of Bundle His-Tawara, *Cardiologia* 5: 189, 1941.

slightly farther advanced on the left than on the right, and a vector (not quite so long as represented) appears, pointing across the septum from left to right. Following Bayley<sup>12</sup> and, in a general fashion, Lewis,<sup>4</sup> this vector can be assumed to produce the Q wave in lead I and lead II in a heart thus rotated, in lead III it initiates the R upstroke. With clockwise rotation of the heart, this vector is supposed to initiate  $Q_3$ , as will be illustrated later.

We do not insist on this mechanism of production of the Q wave. When  $Q_1$  is present in right bundle branch block, it is not larger than the normal Q wave. If the Q wave is formed by the septum at all, left ventricular effects alone must rapidly

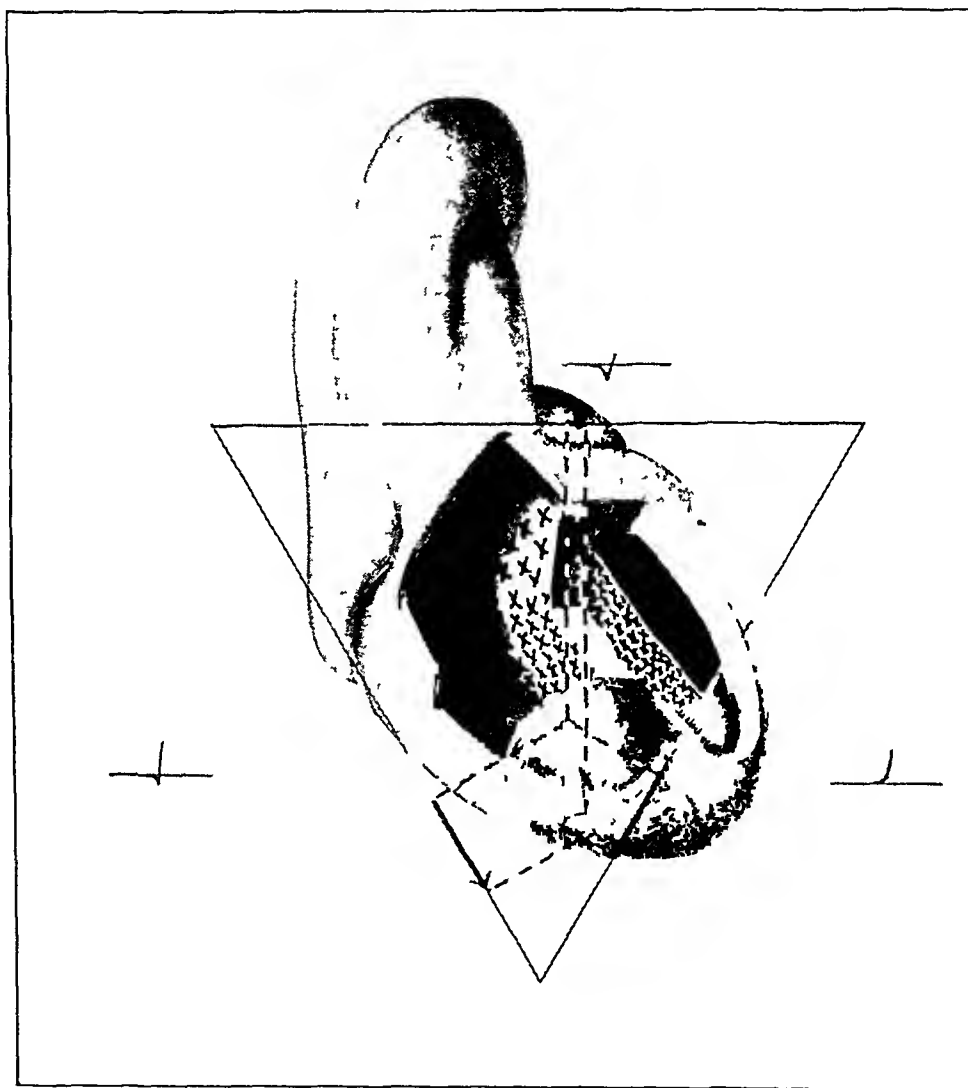


Fig 3—Activation has occurred about 0.01 second later than in figure 2. Complete polarized shells are shown on the endocardial surfaces of the ventricular apices. The septum is approaching full activity on both sides (see text). The vector is the resultant of the two apical shells, that on the right being regarded as larger. It actually has a more forward direction than the picture appears to show. The right shell is larger than the left because impulses travel less far to reach the right, than the left, side of the apex.

produce a vector which opposes it and brings it to an end. On the other hand, as figure 3 shows, the next stage in activation of the subendocardial surfaces of the two ventricles is the formation of polarized shells within the ventricular apices.

12 Bayley, R. H. Theoretical Genesis of Q as Observed in the First Three Standard Leads of the Electrocardiogram. A Preliminary Report, *J Trop Med* 41:144, 1938.

Since right bundle branch block does not appreciably modify  $Q_1$ , it may be formed by the apical part of the septum and left ventricle, rather than, as Bayley has stated, by the anterior basal portion of the septal wall on the left side. Since  $Q_1$  is typically abolished by left bundle branch block and not by block of the right branch, it is clearly a left-sided effect.

The foregoing conclusion fits fairly well the analysis reported by Hoff and Nahum for the dog's heart. It is probable from their experimental results, however, that  $Q_1$  in the dog, although probably initiated subendocardially, is contributed to by some posterior portion of the cardiac wall after the impulse has penetrated

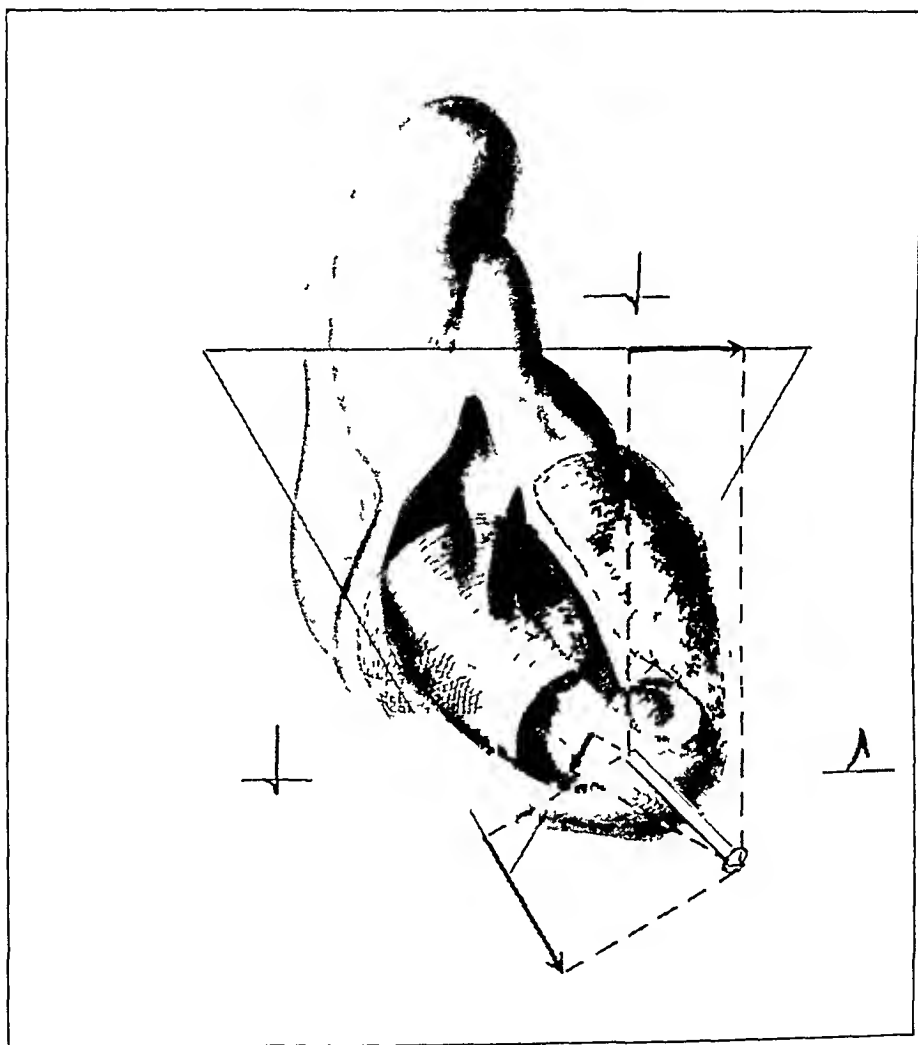


Fig 4—This stage shows that the impulses have broken through the ventricular walls anteriorly and apically. Elsewhere a large shell has formed in both ventricles, the endocardial activation of which is nearing completion. The vector is the resultant. This follows figure 2 after about 0.02 second. Septal shells are omitted in this figure because of difficulty of representation. In this figure and in the succeeding two figures the margin of the polarized shell of the left ventricle should have been shown extending to the epicardial surface except at the base.

the left ventricular apex. It is unlikely, because of the small size of  $Q_1$  in most human records, that this often happens in man. In man the  $Q$  wave is typically initiated before impulses have penetrated the ventricular wall at any place.

Figure 3 follows figure 2 by about 0.01 second, but is about 0.015 second after the beginning of septal invasion. The septal polarized shells are now

practically complete (although shown as if somewhat incomplete), and shells have been formed within the ventricular apices. The electrical effects of the shells on the two sides of the septum nearly balance each other. The two vectors, one for the right and one for the left ventricular apex, may be summated to give a single resultant vector which points downward, forward and slightly to the left when the heart is in this position. The Q wave has already been completed. The distribution of the electrical potential fields is such that  $R_1$  has just begun,  $R_2$  is well on its way upward and  $R_3$ , initiated by the Q effect, is rising sharply.

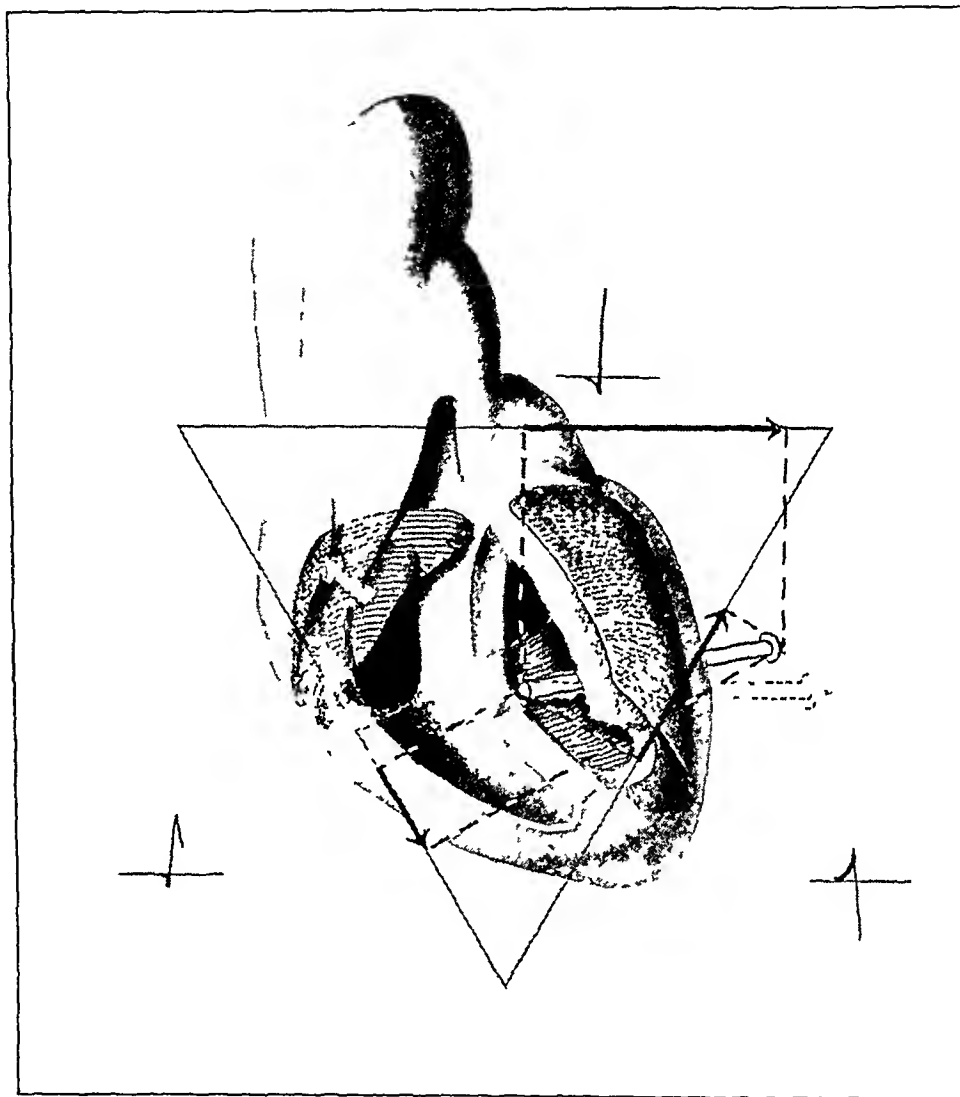


Fig 5—About 0.01 second after figure 4 and 0.04 second after the beginning of ventricular activation the shell has disappeared from most of the right ventricular wall and has slightly diminished in area in the left ventricle. The solid vector is the resultant. The vector now points somewhat backward, as well as to the left.

No further comment on this figure seems needed, except to note that in the dog, at least, even at the stage given, the impulses may already fully have penetrated the anterior ventricular walls near the septum, particularly on the right. In the dog, also,  $Q_1$  may still be in progress at about this stage.

As Harris<sup>6</sup> demonstrated, confirming Lewis and Rothschild's<sup>8</sup> calculations, once the subendocardial spread of the impulses has begun, the progress is rapid. In figure 4, only 0.010 second later than figure 3 and 0.025 second after the impulse began to invade the septum, the excitation has traveled to involve the major part

of the subendocardial surface of the two ventricles. It has also penetrated to the subepicardial surface of the right ventricle, anteriorly, apically and upward for a distance near the septum, and less extensively the impulse has penetrated the wall just above the apex of the left ventricle. Active muscle, just like inactive muscle, is electrically inert. The polarized shells within the walls of the two ventricles are shown in the figure. The shells have openings, as already indicated at and near the apex, and they have not yet grown to involve the basal ventricular margins. The resultant of the electrical effects of the polarized shells is shown by the arrow which points downward, to the left and a little forward. The effect of this vector

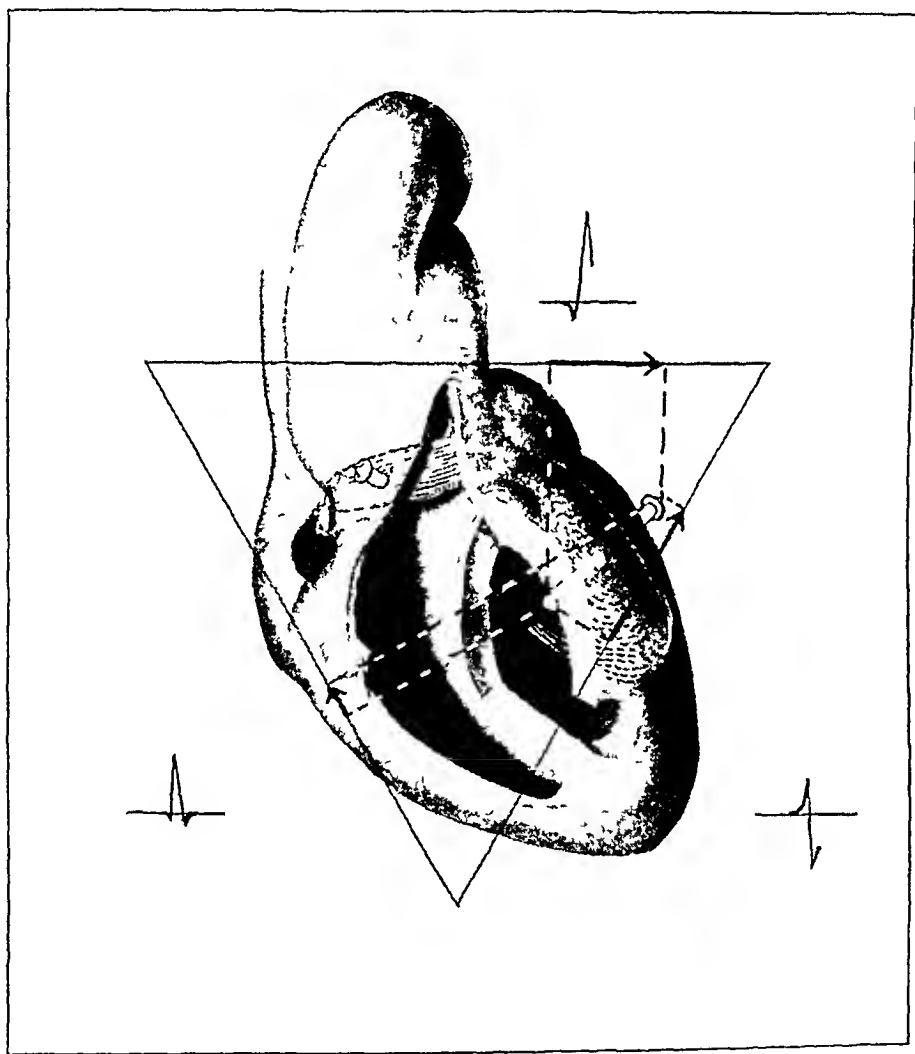


Fig 6—A still later stage, about 0.02 second after figure 5. The posterolateral left ventricular shell is dominant.

is also shown as projected on each lead. Thus,  $R_1$  has climbed higher, and  $R_2$  has risen less, while the downstroke of  $R_3$  has begun, since this vector in the counterclockwise rotated heart points nearly at right angles to the line of lead III.

At this stage possible electrical effects from the interventricular septum may be neglected, since the two septal vectors, one on each side of the septum, are opposite in direction and counterbalance each other.

Figure 5 shows a still later stage, about 0.04 second after the beginning of the QRS complex. The thin-walled right ventricle is depolarized except for its basal margin and the region of the pulmonary conus. The relatively thin apical wall of

the left ventricle is also fully active, but a shell is still present in the lateral and basal walls, as shown. The shell in the right ventricle produces a vector, of moderate length, which points upward, forward and toward the right. The much larger shell in the left ventricle produces a vector which points almost directly to the left and somewhat backward. The vector resulting from the two is drawn in solid lines. It causes  $R_1$  to reach its apex. Meanwhile  $R_2$  is descending, and  $S_3$  is already far on its downstroke. As we shall show later, a clockwise rotated heart may not show an  $S_3$ , our description applies to the rotation shown in the figure. We may say here that moderately deep  $S_3$  waves and so-called "left axis deviation" are not

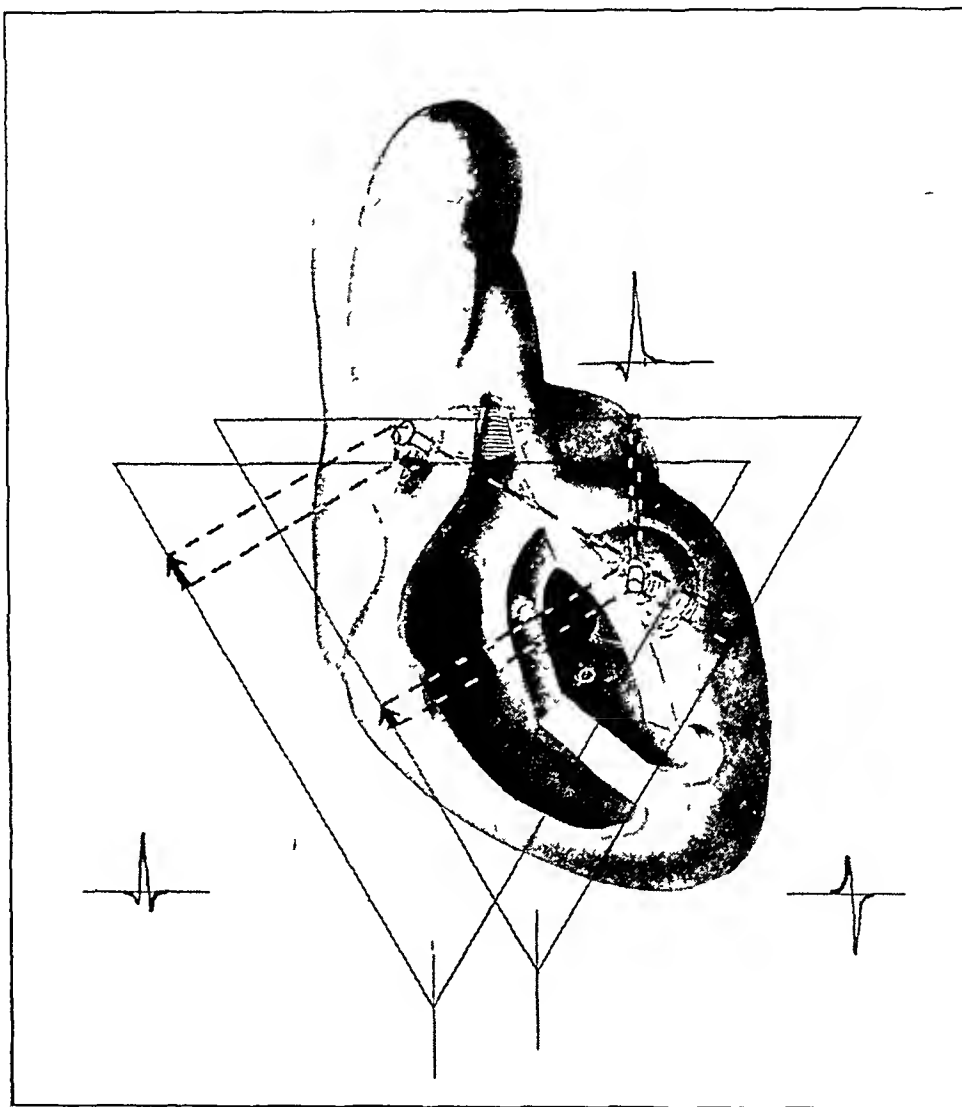


Fig 7—Nearly the whole ventricular musculature has become active. The vector in the conus is shown projected on one triangle. The left ventricular vector is projected on the other. The small central arrow is their resultant. At this stage one or the other vector may have disappeared. If the left ventricular vector vanishes first, an S wave appears in lead I, if the conus vector vanishes first, there is no S wave in lead I. The QRS complex is completed, as shown, in less than 0.01 second after this stage. The deflections on all figures in this paper are drawn to scale (3:1).

unusual in persons of sthenic build, whose hearts are placed in an average position with reference to rotation around an anteroposterior axis.

Figure 6 shows a still later stage about 0.02 second after figure 5. The two vectors summate to give the vector shown for the left ventricle. Thus,  $R_1$  is descending,  $S_2$  is being formed, and  $S_3$  is on its ascending limb.



The stage shown in figure 7 is the last one to be represented. Here the right ventricular vector (now limited to the pulmonary conus) and the left ventricular vector in the basal, posterolateral left ventricular wall are separately projected on the lines of the leads. The central arrow is then resultant. In the dog the conus region is often, and perhaps usually, the last to be activated, but Harris found the base of the left ventricle to be just as late in the monkey. Very likely there are individual variations in lateness, both in human beings and in animals, and certainly there is considerable variation in the terminal parts of the QRS in human beings. If the left ventricular vector is last in figure 7, no  $S_1$  will appear. If the conus is equally late, or later, there will be an  $S_1$ . Hoff and Nahum attribute  $S_3$  to the anterior surface of the right ventricle after activation of the posterior surface of the left ventricle. The results of Lewis, of Harris and of others all show that the anterior surface of the right ventricle in question must be the region of the conus, since it is the only right ventricular region not fully activated at the time  $S_3$  in the dog is formed. In the dog, the heart of which is not rotated as in our figures, the conus, therefore, almost certainly contributes to  $S_3$  and may alone be responsible for it, though other regions have not rigorously been ruled out. In man, depending on the position of the heart, the conus may contribute to  $S_1$  or to  $S_3$  or to both. It may be added that a precordial lead from over the region of the conus in man usually shows a QRS complex with a terminal, upright (positive) deflection. This deflection is most plausibly to be ascribed to activity of the conus. Electrical exploration of the chest in this region may help elucidate the frequency and degree of conus contribution to the QRS complex in man.

As the vectors of figure 7 die away, the QRS complex becomes complete. The several vectors we have drawn represent stages in the development of the vectorcardiogram, which was mentioned in the introduction.

If the wall of the right ventricle were thoroughly warmed, the effect would be considerably to increase the velocity of the impulses, so that, for example, the shell shown in figure 4 would be stripped away early at a time when the vector produced by the left ventricle is near its maximum magnitude. The effect would be greatly to increase the height of the R wave. This has, in fact, been accomplished by Nahum, Hoff and Kaufman,<sup>7a</sup> in the dog in a beautiful series of experiments. Conversely, cooling the right ventricle will cause the shell to persist so long that full activation of muscle of the left ventricular wall occurs before full activation of the right wall. Consequently, the R vector of the left wall is almost fully counterbalanced by the persisting shell in the right wall, and the R waves are greatly reduced in height. Analogous, though reverse, results were found by Nahum, Hoff and Kaufman<sup>7a</sup> to follow warming and cooling of the left ventricular wall.

In an earlier paper Kisch, Nahum and Hoff<sup>13</sup> reported that injection of potassium chloride solution into a ventricular wall had little or no effect on the electrocardiogram. In contrast, when the solution was applied to a small epicardial region, deviations of the RS-T segment appeared. The authors, therefore, concluded that the electrical variations recorded by the electrocardiograph were produced exclusively, or almost exclusively, on or by the epicardial surface. No such conclusion is justified, since the intramural injection of potassium chloride solution produced depolarization of a region of muscle surrounded on all sides by normal muscle and the electrical forces are fully counterbalanced, in much the same way that the left ventricular vector producing  $R_1$ , for example, is partly counterbalanced or offset by the vector simultaneously present in the right ventricle.

13 Kisch, B., Nahum, L. H., and Hoff, H. E. The Predominance of Surface over Deep Cardiac Injury in Producing Changes in the Electrocardiogram, *Am Heart J* 20 174, 1940

Our conception of the mechanism of production of the QRS complex is not new. Aside from details, it is the type of explanation advanced by Lewis and by many subsequent investigators. So far as we know, however, this is the first attempt to present the explanation in some detail. As further evidence, aside from the obvious implications of the experiments quoted, we refer the reader to figure 8, an electrocardiogram of the type described, obtained on a healthy male subject aged 23. The form of the QRS complex in each lead and the relative times of inscription of the various peaks are especially to be noted and compared with the QRS complexes of figure 7. There is a notching of  $R_3$  in this case, which is not accounted for by our vectors. A similar notch is not uncommon in records of this type, and it may be ascribed to an abrupt shift in vector direction between vector 3 and vector 4, probably caused by normal irregularities in the growth and decline of the right

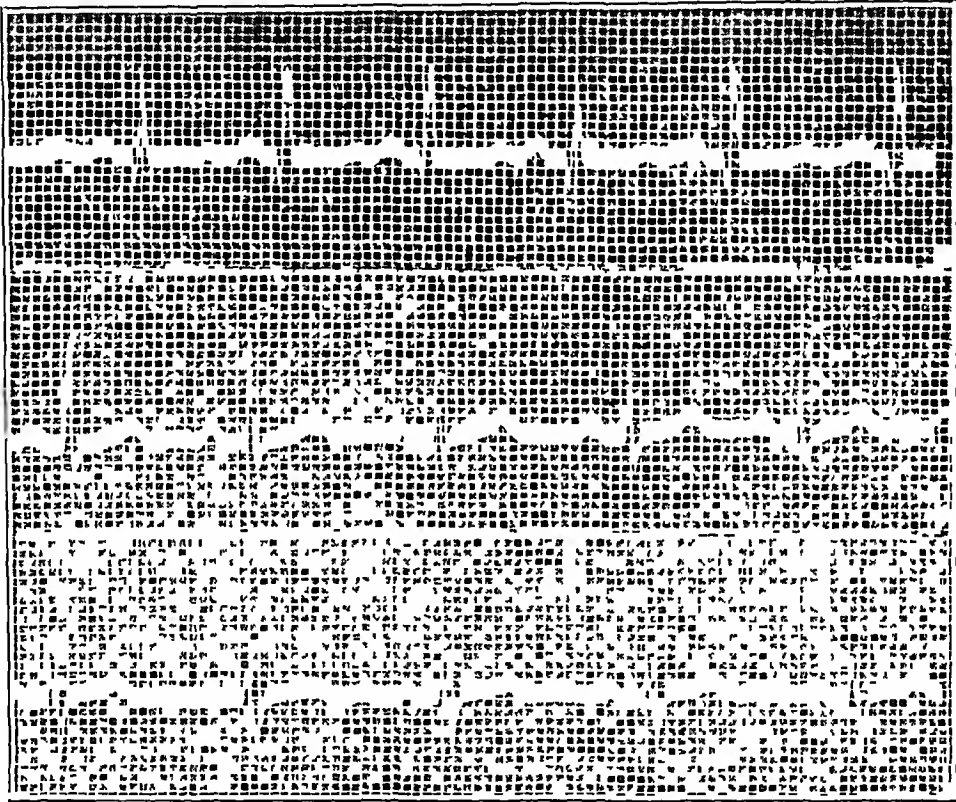


Fig 8—An electrocardiogram made on a normal, recumbent, medical student aged 23. The QRS complex is discussed in the text. In lead I, and less successfully in the other leads, the heart was “voluntarily” accelerated. It is worth noting that the Q-T interval did not at once fall to the duration “normal” for the heart rate in lead I. This case is further discussed by Ashman and Byer.<sup>15</sup>

and the left ventricular vectors which summate to give vectors 2, 3 and 4. Phenomena of this sort, which are also responsible for the frequently seen splintering of low QRS complexes in lead III, will usually be visible only on waves of low amplitude and are, no doubt, subject to individual variation. Obviously, these minor, more or less individual peculiarities cannot be considered in any schema as simple as the one we present. Returning to the subject of figure 8, there is, unfortunately, no way to be certain that his heart is, in fact, rotated counterclockwise on its long axis since this cannot be determined fluoroscopically. In support of our assumption that records similar to figure 8 indicate that the heart is rotated counterclockwise on its long axis as compared with the average position of the heart,

we may refer to the old observations of Meek and Wilson<sup>14</sup> They found that rotation of the dog's heart on its long axis produced changes in Q and S waves similar to those we have pictured for man Aside from these experimental observations, it is known that dilatation of the right ventricle, which usually leads to clockwise cardiac rotation, often causes a deepening of S<sub>1</sub> and of Q<sub>3</sub>, whereas the reverse effects are commonly produced by left ventricular hypertrophy And it is also a matter of common observation that in early infancy, when the right ventricular wall is nearly as thick as the left one, the electrocardiogram is of the type ascribed to marked clockwise rotation in the adult

#### THE ELECTROCARDIOGRAPHIC EFFECTS OF CARDIAC ROTATION ABOUT THE ANTEROPOSTERIOR AND THE LONGITUDINAL AXIS

In the previous section we have traced the electrocardiographic consequences of the spread of the excitation wave through the ventricular muscle To render the diagrams clearer, we chose a rather extreme position of counterclockwise rotation of the heart on its long anatomic axis as viewed from the apex We shall now proceed to an examination of the effects produced by rotation of the heart to other positions about the anteroposterior and the longitudinal anatomic axis A further word will be said at the end of this section about the effects of cardiac rotation about a transverse axis Although different thoracic forms and cardiac positions may modify to some extent the diastolic shape of the ventricles, the electrical effect is apparently slight, and we have not attempted to take such influences into account Needless to say, a change in intrathoracic cardiac position cannot be supposed to influence the sequence of ventricular activation

Figure 9 illustrates the electrical effects of rotation of the counterclockwise rotated heart about its anteroposterior axis Figure 9 *A* recapitulates in one figure the series of stages of activation which have already been described in connection with figures 2 through 7 The successive vectors at the six chosen stages of the previous section are numbered in sequence and are represented as if radiating from a common origin The dotted line, beginning at the origin and connecting the tips of the arrows representing the vectors, is the approximate vectorcardiogram which would be recorded from this heart It may be repeated that the ventricular vectorcardiogram is produced by the continuous series of instantaneous electrical axes which inscribe the ventricular electrocardiogram, and of this infinite series, we have chosen just six stages as representative

Since the stages of activation shown in figure 9 *A* were described in the previous section, we may turn to figure 9 *B*, which shows the same heart, with the same degree of counterclockwise rotation about its long axis, after it is rotated about its anteroposterior axis to a more transverse position It is evident that if the rotation is confined to the single axis, the effect will be simply a tilting upward of the vectorcardiogram toward the left shoulder and equal rotation counterclockwise of all the vectors about the anteroposterior axis The electrocardiographic effects of this rotation, as compared to figure 9 *A*, are mainly to reduce the amplitude of R<sub>2</sub> and R<sub>3</sub> and to deepen S<sub>2</sub> and S<sub>3</sub> At the same time Q<sub>1</sub> may be reduced and Q<sub>2</sub> abolished, although, as stated previously, the true Q wave is less consistent than the other deflections

Our own fluoroscopic and roentgen observations have shown hearts in sthenic persons, the silhouettes of which were similar to that of figure 9 *A*, which yielded

14 Meek, W J, and Wilson, A The Effect of Changes in the Position of the Heart on the QRS Complex of the Electrocardiogram, Arch Int Med 36 614 (Nov) 1925

similar electrocardiograms. It is, of course generally known that transversely placed hearts are likely to produce records similar to that of figure 9 *B*. It has been stated that supposed discrepancies, namely, hearts in an average position (as fig 9 *A*) yet showing a "left axis deviation," demonstrate the inutility of vector analysis. On the contrary, the signs of rotation revealed by the electrocardiogram are often useful, since they may reveal rotations due to pathologic conditions, some of which may be transient, as in massive pulmonary embolism.

Figure 9 *C* shows the same counterclockwise rotated heart, rotated in a clockwise direction about the anteroposterior axis. Such a combination of rotations is

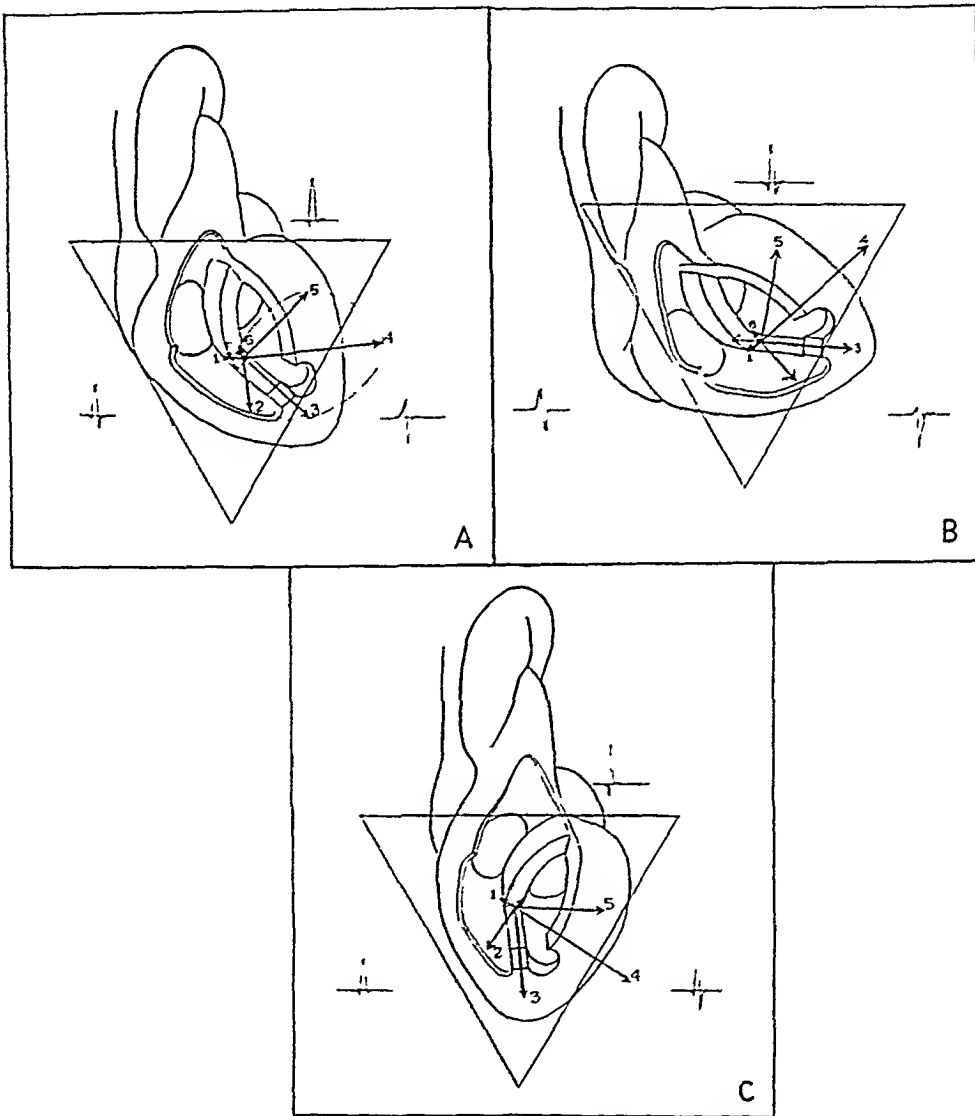


Fig 9—See text for explanation. Note that  $S_1$  and the similarly timed wave in lead III show two alternative amplitudes.

unusual under normal conditions in the human heart but may occur in some cases of hypertrophy of the left ventricle. The electrocardiogram, compared with that of figure 9 *A*, shows a  $Q$  wave in all leads, an augmentation in the height of  $R_3$  and some decrease in  $R_1$ , together with shallower  $S_2$  and  $S_3$ .

We may now turn to the evidently more common condition, namely, slight counterclockwise rotation from the "average" position about the longitudinal axis. The "sthenic" position of such a heart is shown in figure 10 *A*. In contrast to the more strongly rotated heart,  $S_3$  is less deep and  $S_2$  may be absent. Other changes are slight. It may be observed, however, that vector 6, which produced a small

$S_1$  in figure 9 *A*, may here be directed almost straight backward, producing practically no effect. As we have pointed out, since the smaller  $S$  waves may be produced either by the conus or by the posterior, basal, left ventricular wall or by both, depending on the relative times of full activation of these regions, variability in small  $S$  waves is to be expected. Such variability is actually observed.  $S_3$  in figure 9 *A*, on the other hand, is a posterolateral left ventricular effect, produced in the region which contributes to  $R_1$ , and is not subject to variation in the same way.

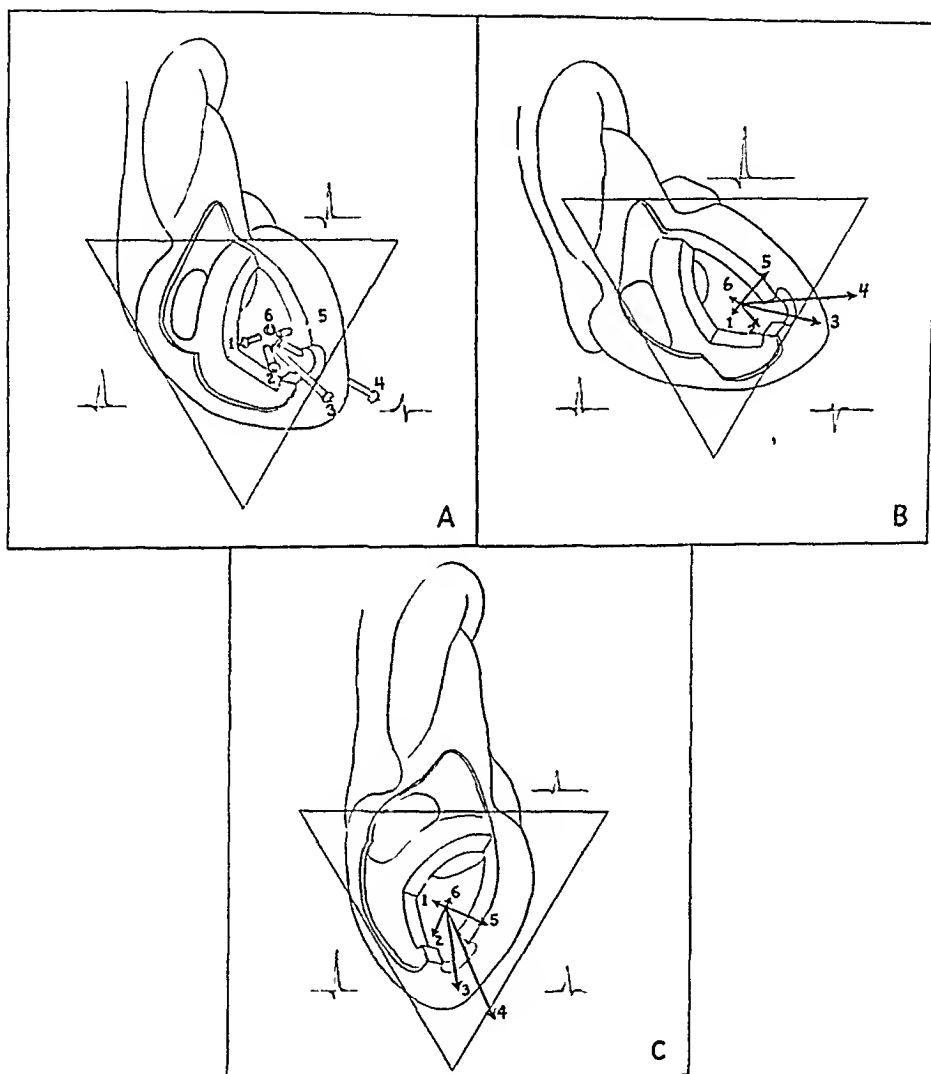


Fig 10—See text for explanation

Figures 10 *B* and *C* illustrate, respectively, the effects of rotation to a more transverse and to a more vertical position. The transversely rotated heart shows a deeper  $S_3$  and a low  $R_3$ , and  $S_2$  is likely to be present.  $R_1$  is higher. The other changes from the "sthenic" position are unimportant. The vertical heart (fig 10 *C*) reveals a higher  $R_3$  and a less deep  $S_3$ , together with a much lower  $R_1$ . This record is not common.

Figure 11 shows a series of hearts which are rotated slightly in a clockwise direction from the "average" about the longitudinal axis. Probably more human hearts fall into this group than into any other single one, though it must also be stated that vertical hearts in particular, show this type of record, whereas trans-

verse hearts are more likely to show some degree of counterclockwise rotation. In contrast to the previous series of rotations, the vectorcardiogram, emerging from the origin, circles now to the left and then to the right and upward, to regain the origin with disappearance of  $S_1$ . We now find in figure 11 *A* that  $Q_1$  is absent and  $Q_3$  is present.  $R_1$  and  $R_3$  are of nearly the same height.  $S_1$  is present, and  $S_3$ , unless contributed by late activity of the conus, is absent.

When this heart is rotated to a transverse position, as in figure 11 *B*,  $R_1$  becomes higher and  $R_3$  lower.  $Q_3$  becomes prominent. This electrocardiogram

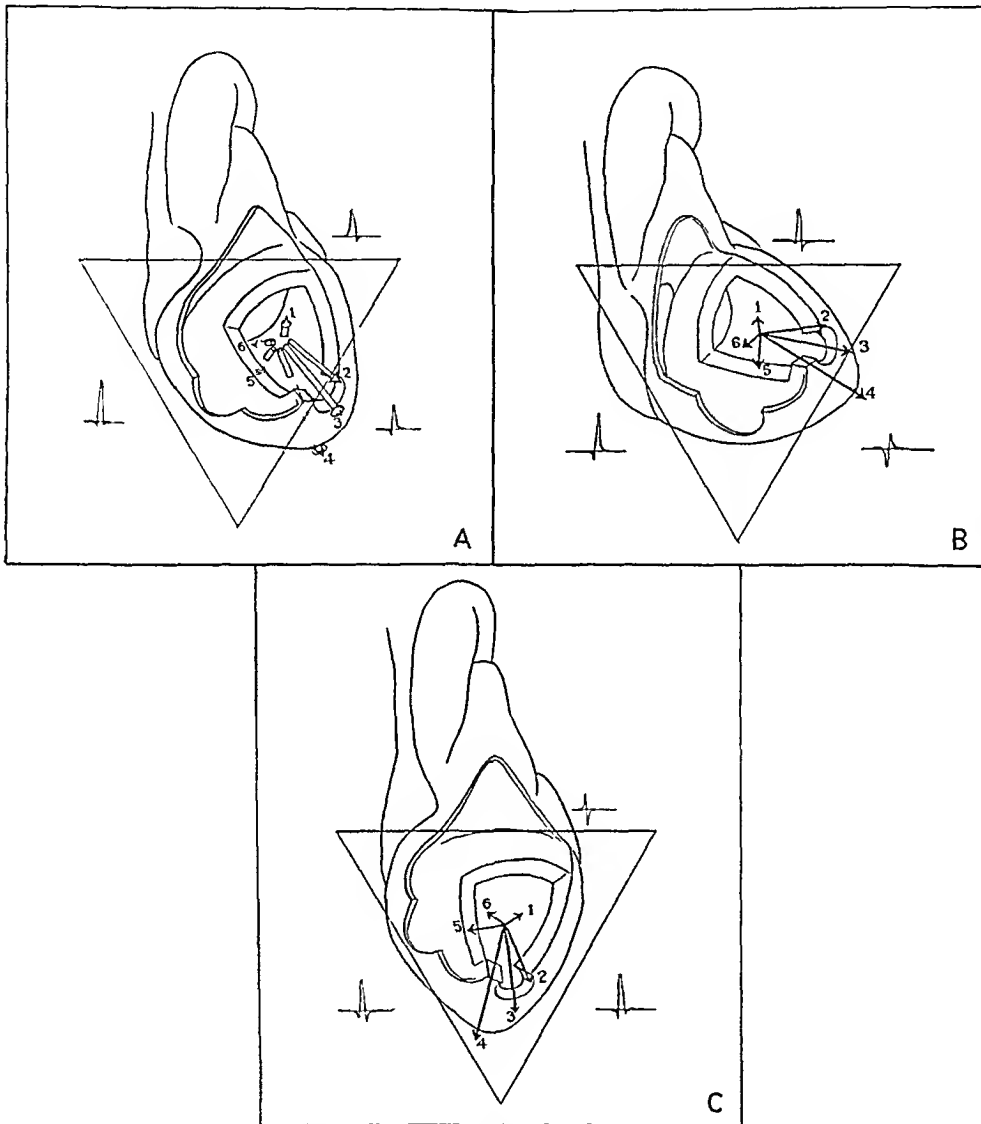


Fig 11—See text for explanation

occurs fairly commonly in obese persons, particularly women perhaps, and in pregnant women. In these persons the electrocardiogram is presumably often made from a heart of the figure 11 *A* type pushed toward or to the figure 11 *B* position.

Another, commoner, picture is that of figure 11 *C*. It is characteristic of tall, slender persons.  $R_1$  is low,  $R_2$  and  $R_3$  are relatively high.  $S_1$  is present, and there are often  $S_2$  and an  $S_3$ , depending on the relative contributions from the posterior, basal, left ventricular wall and the pulmonary conus.

We finally come to the series of figure 12. The heart is here rotated strongly in a clockwise direction, as viewed from the apex. In the "sthenic" position (fig

12 A), except for the depth of  $S_1$ , the picture differs but little from that of figure 11 A. The strongly rotated vertical heart (fig 12 C) shows a relatively high  $R_s$ .

Although the electrocardiograms of figure 12 are encountered in some normal persons, they have a special bearing on the changes which appear in association with massive pulmonary embolism or other conditions associated with dilatation of the right ventricle. Obviously, patients whose hearts are in any position of rotation may fall victim to pulmonary embolism. If the antecedent position was one of considerable counterclockwise rotation (fig 9), only a great degree of dilatation of

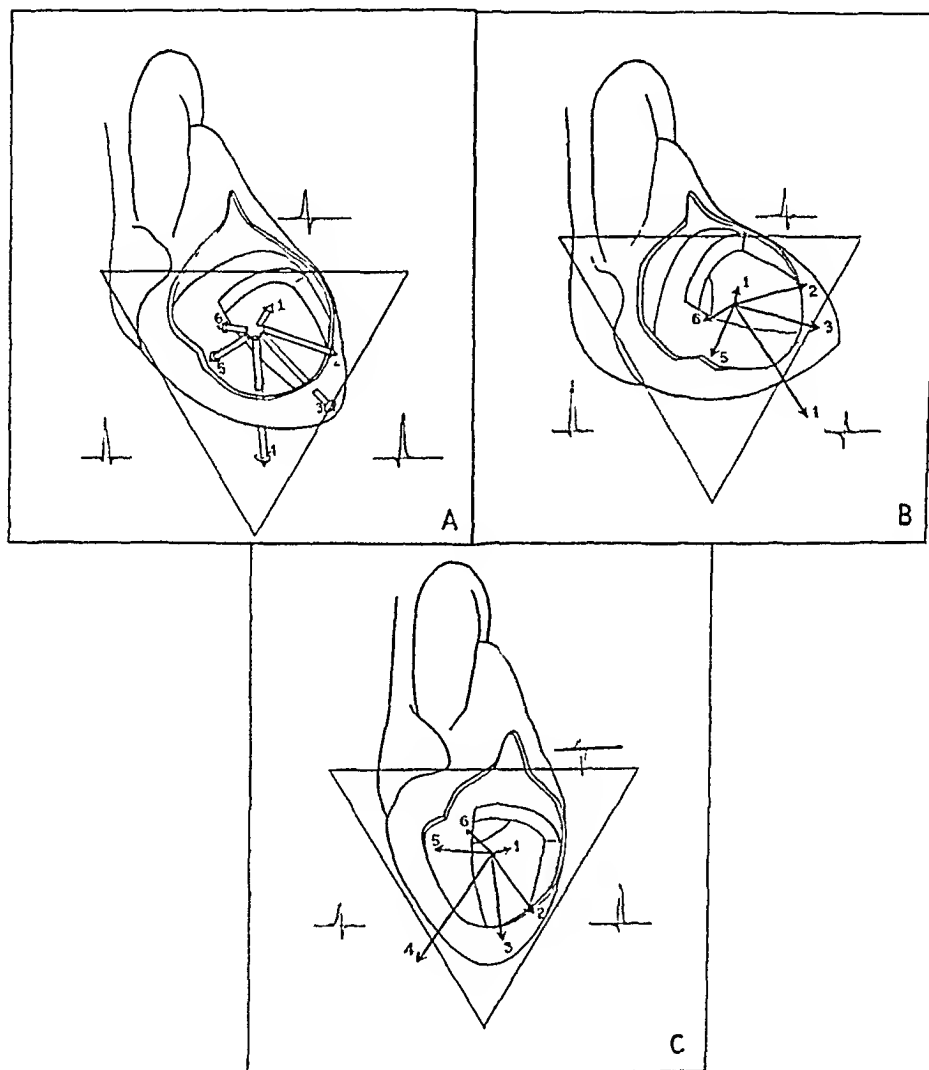


Fig 12—See text for explanation

the right ventricle could produce the picture of figure 12, whereas much less dilatation could rotate the heart of figure 11 to this more extreme position. Undoubtedly, this is one of the factors which prevents the development of the characteristic electrocardiogram in cases of pulmonary embolism. Dilatation of the left ventricle appears to be capable of producing relatively little rotation of the heart about the long axis since the ventricle is free to bulge backward.

The rotations which have been described, both in normal conditions and in conditions which lead to dilatation of the right ventricle, are associated with consistent rotations of the ventricular gradient, resulting in characteristic changes in

the T wave. These have been described in part by Ashman and Byer<sup>15</sup>. A paper to be published<sup>16</sup> shows the cardiac silhouettes of a number of subjects. Almost without exception, we could have predicted the intrathoracic position of these hearts from the electrocardiogram alone.

#### EFFECT OF CARDIAC ROTATION ABOUT THE TRANSVERSE AXIS

The foregoing analysis takes account of electrocardiographic variations resulting from rotation about only two of the three possible axes of rotation, namely, the longitudinal and the anteroposterior. It is evident that in some persons the heart must be relatively vertical, for example, not only with reference to rotation about the anteroposterior axis but with reference to rotation about a transverse axis. Such a person would have a narrow anteroposterior thoracic diameter, as a rule, and would possess a truly so-called "dropped heart". The electrocardiographic effects may be inferred from figure 11 C, which shows a heart rotated slightly clockwise and vertically with respect to the anteroposterior axis. If the apex of such a heart were pushed back or the base pulled forward, vector 1, which points forward and slightly to the left and upward, would point slightly to the left and downward. Consequently no Q wave would appear in any lead, the Q effect now appearing as the beginning of the R waves. This essentially follows the analysis of the Q wave as given by Bayley<sup>12</sup>. At the same time vectors 2 and 3 would point more directly downward, and this would accelerate the upstroke of R<sub>2</sub> and R<sub>3</sub>. Vector 4 points downward, to the right and backward. The rotation will cause it to become shorter, as projected on the frontal plane, so that R<sub>3</sub> will be reduced in height, unless the shortening of vector 4 is compensated for by the lengthening of vector 3. Vectors 5 and 6 will point more nearly directly upward than they do in the figure, and this will deepen the S wave in all three leads. Such electrocardiograms, displaying little or no Q wave, a rather low R<sub>1</sub>, a higher R<sub>2</sub> and a well marked S wave in all three leads, are by no means uncommon. In many instances, at least, they are associated with the postulated body build.

Some electrocardiograms of the type described in the previous paragraph show relatively low R waves in all leads. This cannot be explained on the basis of our diagrams, but it is quite consistent with the experimental findings of Harris<sup>6</sup>. It may be recalled that the wave of excitation reached the anteroapical epicardial surface of one of Harris' monkeys somewhat earlier than in the other. If this early penetration of the walls means that epicardial activation occurs before the shells producing vectors 2 and 3 have expanded within the ventricular wall, then these vectors will be distinctly shorter than they are represented in our diagrams. When such a heart is "dropped" the R waves will be relatively low. As a matter of fact, the observations of Ashman and Byer<sup>15</sup> and the experimental results of Hoff and Nahum obtained on the dog suggest that our vectors 2 and 3 are, in fact, relatively a little longer than they are in reality in many human hearts. We arrived at this conclusion only after our figures were drawn. Had the vectors been made shorter, the effects would be slight except in a few cases, particularly in the case of the "dropped" heart.

A second, fairly large, class of electrocardiograms is similar to those of figures 11 A and C and 12 A and C, but no S wave is present in lead II and R<sub>1</sub> and R<sub>2</sub> are relatively higher. This is the picture which would be produced by pulling the apex slightly forward or pushing the base backward. Vector 4 is lengthened by

15 Ashman, R., and Byer, E. The Normal Human Ventricular Gradient. I and II, *Am Heart J* 25: 16 and 36, 1943.

16 Ashman, R., Gardberg, M., and Byer, E. To be published.



this rotation about the transverse axis, vector 5 may point more toward the galvanometer electrode on the left leg than toward that on the right arm, and vector 6 points nearly at right angles with the line of lead II. In a few instances we have been able to observe that subjects whose records are of this type are distinctly deeper chested than those with "dropped" hearts. Extensive future correlation is needed, however, before we can assert that the suggested differences are generally consistent.

A third type of electrocardiogram is illustrated by our series only as an alternative form in figure 9 *B* and shows a *W* complex in lead I, namely a distinct  $Q_1$ , an  $R_1$  which may be high and a distinct, but not deep,  $S_1$ . In lead III there are a low *R* wave, an *S* wave, the depth of which is variable, and a final upright deflection (*M* complex). When  $S_3$  is more than 2 or 3 mm deep, at least, a comparison of the *QRS* axis and the ventricular gradient indicates that the heart is rotated more or less counterclockwise. This may represent a heart of the type shown in figure 10 *A* or *B* or 9 *A* or *B* but with the apex farther forward or the base farther back. Vector 5 and the pulmonary conus could still write an  $S_3$ , but vector 6, now pointing downward and to the right, being produced by late activation of the conus, could give a final *S* wave in lead I and a final upward deflection after the inscription of  $S_3$ . We have not been able to confirm this suggestion, which at best might be difficult to prove by fluoroscopic or other evidence.

Only one other fairly common type of electrocardiogram remains, which is not covered by our series. It is the type showing a *Q* wave in all three leads and no *S* wave. Such a picture will result if the base of a nonrotated heart is tilted backward.

Our diagrams also fail to illustrate an intermediate type, with no rotation on the long axis, namely, what we call the average position of rotation for want of a better term. At this position the plane in which the vectors lie will be seen edgewise. If the heart is slightly transverse, the larger vectors, namely, vectors 2, 3, 4 and 5, may have a direction at right angles to the line of lead III. Under these circumstances, a slight deviation of the vectors, one out of the common plane to one side, another a little bit to the other side, etc., will produce a splintering of a low  $QRS_3$ . This is, of course, a perfectly normal phenomenon as every electrocardiographer knows.

#### COMMENT

In a paper by Ashman and Byer,<sup>15</sup> which studies the relation between the *QRS* complex and the ventricular gradient, the conclusion is reached that the mean or average, electrical axis of the *QRS* complex in a few normal hearts may point directly backward or even backward and slightly upward. This conclusion would have seemed incredible to us, had it not been for the results of the present study. It will be noted, however, that vectors between 2 and 3 in our figures point relatively forward for about 0.02 second, whereas vectors between 4 and 5 point relatively backward for at least 0.03 second. Furthermore, the average length of the vectors between 4 and 5 in three dimensional space is at least double the average length of vectors between 2 and 3. Hence, since the larger vectors point relatively backward for a longer time, and the shorter vectors point relatively forward for a shorter time, the mean electrical axis of the *QRS* complex will point relatively backward, that is, backward, downward and usually to the left. But in some "dropped" hearts, particularly when anterior subepicardial activation is relatively early, the mean *QRS* axis may point straight backward at right angles to the frontal plane or even backward and upward. When the mean axis is indicated on a good model of a heart and the heart is placed in a vertical position, this is easy

to visualize. In support of this conclusion is the picture often seen after anterolateral infarction, which has eliminated much of the left ventricular muscle which normally contributes to vectors 2 and 3.  $QRS_1$  is low, often with a deep Q wave;  $R_2$  and  $R_3$  are low, and there are a deep  $S_2$  and  $S_3$ . The mean electrical axis under such circumstances points backward and upward, its upward direction being greater than in any normal hearts. We have observed axes which point backward and slightly upward in conditions, such as bronchial asthma, which, by one mechanism or another, render the heart more vertical. We do not intend to deny by this analysis, however, that some distortion of the electrical fields by the thoracic configuration and by the lungs may not contribute a little to the relatively backward direction of the mean QRS axis. We do believe that such factors are of secondary importance.

Finally, we may inquire into the bearing our analysis has on the moot question of the validity of the Einthoven triangle method of determining the directions of the electrical axes. It may be pointed out again that we exercised considerable care in fixing the orientation relative to each other of the ventricular walls and their relative thickness in different regions. From roentgenograms the range of variation with respect to the anteroposterior axis is well known. The degrees of rotation around the longitudinal axis cannot be directly determined from a roentgenogram, and the amount of rotation is largely inferential. Our clockwise and counterclockwise rotations probably represent the extremes under normal conditions. The vectors have been drawn in accordance with the best evidence from investigations on animals and human beings, and their approximate correctness is supported by the comparison of the QRS axis and the ventricular gradient. It is, of course, impossible to be sure that the various rotations suggested by the electrocardiogram of any subject are actually present. Nevertheless, the correspondence between the constructed electrocardiograms and those actually observed is close. It is so close, in fact, that the presumption is strong that the direction of a vector as recorded is nearly its true direction in a large majority of persons. Wilson and Johnston<sup>1</sup> were evidently of the same opinion. It may be recalled that there are 360 degrees in a circle. Even if the recorded direction of a vector is often in error by  $\pm 10$  degrees, which seems to be a reasonable limit of error, this 20 degree range is only 11.2 per cent of a half circle, as small an error as is found in other determinations or measurements of admitted usefulness in medicine. Even if there were no error (which is impossible except as a rare coincidence), the absolute direction of the axis is of far less importance than the comparison between the direction of one vector, for example, the mean QRS axis, and of another vector, such as the ventricular gradient. It is reasonably certain that the error which affects the one will affect the other almost equally and in the same sense. In this case it becomes irrelevant whether the directions indicated are quite accurate. It has been stated that the fact that a patient's electrocardiogram often fails to reveal a left axis deviation in the presence of left ventricular hypertrophy proves that vector analysis is invalid. On the contrary, vector analysis, with roentgen support, has shown that not all patients with left ventricular hypertrophy should show left axis deviation, and the analysis has enabled us much more accurately to recognize the hypertrophy in the absence of the deviation. This will be considered in a later paper.

It is, of course, true that there are certain conditions in which the direction of the vector as determined cannot safely be regarded as its approximately true direction. These conditions include some cases of pulmonary disease, pleural effusions, pneumothorax, extreme scoliosis or kyphosis and possibly adhesive peri-

carditis. In bronchial asthma during an attack, during deep inspiration by a normal subject and possibly in pericardial effusion, the error may be magnified. The presence of fluid in the thorax or abdomen will reduce the magnitude of the vectors. However, the changes produced by respiration, as illustrated, for example, in Master's<sup>17</sup> useful book, can be fully explained on the basis of the changes in cardiac position.

#### SUMMARY

An analysis is presented of the QRS complex of the human electrocardiogram and of the variations in that complex which should appear when the heart is rotated to different positions within the thorax. Among different subjects there are considerable differences in the cardiac position within the thorax, and the effects of these differences are explained. In making the analysis we have correlated (1) experimental findings in the experimental animal, (2) known effects of rotations of the heart in man produced by normal procedures or certain pathologic conditions, (3) known effects of bundle branch block and of infarction in man, and (4) information derived from studies of precordial leads. Less attention was given to the conflicting anatomic studies of the Purkinje system. In order to visualize the electrical events in three dimensional space, clay models have been used.

The reader must judge for himself how successful the analysis has been. We are convinced that in a large majority of subjects the directions of the electrical axes as revealed by the limb leads and as projected on the frontal plane are correct within  $\pm 10$  degrees, and the usual error may be less than this. It is pointed out that even if the error should be greater the value of vector analysis is not thereby impaired in its more important applications.

Mr W. B. Stewart, of the art department of the School of Medicine, made the figures illustrating this paper.

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<sup>17</sup> Master A. M. *The Electrocardiogram and X-Ray Configuration of the Heart*, ed. 2, Philadelphia, Lea & Febiger, 1942.

# PHYSICAL THERAPY APPLIED AT HOME FOR ARTHRITIS

A FOLLOW-UP STUDY, WITH A SUPPLEMENTARY SUMMARY OF THE  
SEDIMENTATION RATE OF ERYTHROCYTES IN TWO  
HUNDRED AND TWENTY-NINE CASES  
OF ARTHRITIS

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In the general therapeutic program outlined for the patient who has arthritis physical therapy has come to play one of the central roles. The physical therapeutic measures, considering the usual chronicity of the types of arthritis treated, must be applied persistently and patiently over a long period. It can be fairly stated that most likely in every case of chronic arthritis home treatment with physical measures finds a place, either as a less elaborate continuation of the beneficial measures carried out in a physical therapy department by trained personnel or as a primary home regimen of simple physical measures. Because of the chronicity of the more common types of arthritis and because the average patient with the chronic form of arthritis is unable financially to continue with indefinite institutional treatment, an organized plan was developed at the Mayo Clinic for encouraging arthritic patients to carry out simple physical therapeutic measures in the home under the supervision of physicians in their home localities. The three main groups of physical measures employed are (1) thermal measures, including heat, cold and contrast baths, (2) massage and manipulation, and (3) exercise, including general postural training. The specific physical procedures advised for application at home, as adapted to the individual case and to the varying home facilities, have been considered in detail in previous articles<sup>1</sup>

Many and varied are the ways of utilizing each of these three groups of essential measures, and it is important that the arthritis in each case be considered from the standpoint of causation, type, severity, duration, joints involved and expected results and then individualized treatment be planned, if real and lasting benefit is to be expected from physical therapy. For several years a plan has been in effect at the clinic whereby every arthritic patient seen by a physician in the Section on Physical Therapy is prescribed for individually and is given a minimum of one instructional treatment by a trained technician. The patient is instructed during this demonstration treatment in just how he is to carry on treatment at home. A few additional instructional treatments are recommended when this fits in with the patient's temporal and financial economy, in addition, on dismissal, each patient

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1 (a) Hench, P S. Chronic Arthritis, in Barr, D P. Modern Medical Therapy in General Practice, Baltimore, Williams & Wilkins Company, 1940, vol 3, pp 3298-3397. (b) Hench, P S, Bauer, W, Boland, E, Dawson, M H, Freyberg, R H, Holbrook, W P, Key, J A, Lockie, L M, and McEwen, C. Rheumatism and Arthritis. Review of the American and English Literature for 1940 (Eighth Rheumatism Review), Ann Int Med 15 1002-1108 (Dec) 1941. (c) Krusen, F H. Physical Therapy in Arthritis, with Special Reference to Home Treatment, J A M A 115 605-615 (Aug 24) 1940, (d) Physical Therapy in Arthritis, New York, Paul B Hoeber, Inc, 1937

is given detailed exact written instructions. In other words, physical therapy is prescribed as individually and specifically as any other medical or therapeutic measure.

It is recommended that whenever possible patients should have professional physical therapy twice a week to supplement and further guide the home routine. In the majority of cases, however, facilities for these regular weekly or twice weekly additional treatments by a skilled technician are not easily available.

We realize the obvious difficulty of evaluating any treatment for chronic arthritis, especially when such treatment is only one part of a complete well planned program of general treatment which the patient is advised to carry out under the general supervision of his physician. Nevertheless, from the purely practical standpoint we felt it would be interesting and valuable to know whether the patients were carrying out their prescribed treatments and for how long. Also, we wanted to know whether the patients themselves believed that the physical treatments were helping them. After all it is important to know if the patients think the treatment is beneficial. This does not prove that it is, but it does indicate in a sense whether it is worth while to continue prescribing it.

In order to answer these questions a follow-up study was carried out, which proved interesting to us.

TABLE 1—*Types of Arthritis*

Type	No. of Cases	Percentage of Cases
Rheumatoid arthritis	97	44.5
Osteoarthritis	84	38.5
Periarthritis of shoulder	17	7.8
Traumatic arthritis	3	1.4
Psoriatic arthritis	3	1.4
Arthritis of questionable type	3	1.4
Total	207	
Cases not used in detailed analyses	11	5.0
Total	218	100.0

#### ANALYSIS OF DATA

The 346 cases analyzed in the follow-up study were taken at random from a group of several thousand cases encountered during 1940. In each case, a diagnosis of arthritis of some type had been made as one of the major diagnoses and the patient had been seen in consultation in the Section on Physical Therapy. Follow-up data, in response to a questionnaire, have been obtained in 218 of the 346 cases.

The simple distribution of the types of arthritis in this group of 218 cases is given in table 1. There were 97 cases (44.5 per cent) of rheumatoid arthritis in all stages and 84 cases (38.5 per cent) of osteoarthritis in this group. In some cases of the latter disease secondary fibrositis was associated, but the primary difficulty was considered by the clinician in each case to be osteoarthritis. In 3 cases the type of arthritis could not be ascertained definitely. Eleven cases were not used in the detailed analysis of the results in the various types of arthritis for miscellaneous reasons, such as uncertainty as to diagnosis, unrelated coincident illness which complicated the condition, the use of unorthodox treatments in addition to the recommended treatment and the carrying out of the treatment in a definitely unrecommended manner.

The number of cases in which patients carried out the whole treatment recommended or a significant part of it for various intervals of time is given in table 2.

Since the study was made of cases encountered in 1940 and since the questionnaires were sent out in December 1941 and January 1942, a patient could have carried out the treatment for a maximal period of one to two years

Of the whole group of 218 cases studied, in only 16 (7.3 per cent) was the home treatment not carried out at all. This included cases in which patients did take some physical therapy but for various reasons did not follow the recommended home treatment. It is seen further that in about two thirds of the cases the treatment was carried out for three months or longer, and in more than a fourth of them the patients were still doing at least part of the treatment one year or more after leaving the clinic. On the questionnaire the patient was asked merely, "Do you think you were benefited by the home treatment? Please describe briefly." Benefit

TABLE 2—Length of Time Treatment Was Continued at Home

No. of Months	No. of Cases	Percentage of Cases
0-2	61	28.0
3-5	32	14.7
6-11	51	23.4
12 or more	53	26.6
No home treatment	16	7.3
Total	218	100.0

TABLE 3—Subjective Evaluation of Benefit from Treatment at Home

Type of Arthritis	Grade of Benefit					No. Home Treatment No. of Cases	Total No. of Cases
	+3	+2	+1	0	-1		
Rheumatoid arthritis	42 (43.3%)	27 (27.8%)	16 (16.5%)	12 (12.4%)	0	0	97 (100%)
Osteoarthritis	33 (39.3%)	20 (23.8%)	7 (8.3%)	10 (11.9%)	3 (3.6%)	11 (13.1%)	84 (100%)
Periarthritis of shoulder	8	4	5	0	0	0	17
Traumatic arthritis	1	1	0	1	0	0	3
Psoriatic arthritis	3	0	0	0	0	0	3
Arthritis of questionable type	0	3	0	0	0	0	3
Cases not used in detailed analysis	1	0	3	2	0	5	11
Total	88	55	31	25	3	16	218
Percentage	40.4	25.2	14.2	11.5	1.4	7.3	100
	79.8			20.2			

was graded as follows. An enthusiastically favorable reply, more than just "yes," was graded plus 3, a simple unqualified "yes" in answer to the question was graded plus 2, "yes" with qualifications was graded plus 1, no benefit, no harm or a simple "no" was graded 0, and the reply "Harmed by the treatment" was graded minus 1. A detailed analysis of the patients' subjective evaluation of the treatment is given in table 3.

Of all cases, the patients in 3 (1.4 per cent) thought they were harmed by the treatment, the patients in 25 (11.5 per cent) carried out the treatment but thought they did not receive any benefit and the patients in 7.3 per cent, as previously mentioned, did not follow the home treatment at all, which left about four fifths of the cases in which patients reported that the treatment gave them some benefit or relief. In about two thirds of the cases patients answered without qualifi-

cations ("yes" or better) that they were benefited, and in about two fifths they were actually enthusiastic about the benefit they thought they received by carrying out the physical treatment at home

In addition to the evaluation of the benefit in all cases, the benefit obtained in cases of rheumatoid arthritis was compared with that obtained in cases of osteoarthritis. In none of the 97 cases of rheumatoid arthritis did the patients fail to carry out the treatment or think they were harmed by it. The responses in 43.3 per cent of cases were graded plus 3, those in 27.8 per cent were graded plus 2, those in 16.5 per cent were graded plus 1, and those in 12.4 per cent were graded 0 (no benefit). The responses in 39.3 per cent of the 84 cases of osteoarthritis were graded plus 3, those in 23.8 per cent were graded plus 2, those in 8.3 per cent were graded plus 1, those in 11.9 per cent were graded 0, and in 3.6 per cent

TABLE 4—*Effect of Number of Instructional Treatments on Results of Treatment of Rheumatoid Arthritis at Home*

No. of Instructional Treatments	No. of Cases	Treatment Still Continued or Stopped Because of Improvement	
		No. of Cases	Percentage of Cases
One	57	32	56.1
Two or more			
Outpatient routine	14	12	85.7
Hospital routine (3 weeks)	20	17	85.0
Total	39	29	74.4
Total	96*	61	63.5

\* In 1 of the 97 cases of rheumatoid arthritis studied instruction was not given

TABLE 5—*Effect of Number of Instructional Treatments on Results of Treatment of Osteoarthritis at Home*

No. of Instructional Treatments	No. of Cases	Treatment Still Continued or Stopped Because of Improvement	
		No. of Cases	Percentage of Cases
One	69	43	62.3
Two or more	13	9	69.2
Total	82*	52	63.4

\* In 2 of the 84 cases of osteoarthritis studied an instructional treatment was not given

the patients indicated harm from the treatment. In 13.1 per cent of cases of osteoarthritis the patients did not carry out the treatment at all.

The effect of the number of instructional treatments on the results of treatment at home in cases of rheumatoid arthritis and of osteoarthritis is indicated in tables 4 and 5.

The fact that a patient carried out treatment at home for a longer period does not necessarily indicate that the treatments were more beneficial to him, since in a way, if the treatments had to be continued for a longer time, this might have meant that the patient received less benefit than another patient who improved sufficiently in a shorter time to warrant further treatment unnecessary. Furthermore, although it proved interesting to grade the patients' subjective evaluations of benefit from the home treatments, it seemed wise to find if possible a simple, more objective criterion incorporating this thought. As a result, the cases were placed in the following two groups: (1) cases in which patients were considered certainly to have

obtained some degree of benefit, since they were still carrying out the treatment a year after it was prescribed or since they stopped because of improvement, and (2) cases in which patients were considered as not proved to have obtained benefit, since they had stopped treatments for some reason other than improvement. Of course, some cases were included in the latter group in which the patients, though receiving benefit, stopped the treatments for reasons other than improvement, such as lack of equipment, facilities or aid or simple neglect. This was admittedly an arbitrary separation but seemed the simplest gross division of cases into those in which benefit certainly occurred and those in which unquestionable benefit did not occur.

Included in the group of cases of rheumatoid arthritis were those in which patients received only one instructional treatment, those in which the patients had two or more treatments and a third set of cases in which the patients, in general more seriously ill, entered the hospital and followed a definite intensive routine for three weeks, consisting of an average of twenty treatments, with instruction before dismissal on how to continue at home.

Of the cases of rheumatoid arthritis, benefit was obtained, according to our new criterion, in 56.1 per cent of the 57 cases in which patients had the usual single

TABLE 6—*Sedimentation Rates of Erythrocytes*

Sedimentation Rate, Mm./Hr.	Rheumatoid Arthritis		Osteoarthritis	
	No. of Cases	Percentage of Cases	No. of Cases	Percentage of Cases
0-9	14	9.3	23	29.1
10-19	18	12.0	31	39.2
20-29	18	12.0	19	24.1
30-39	19	12.7	4	5.1
40-99	63	44.0	2	2.5
100 or more	15	10.0		
Total	150	100	79	100

instructional treatment, in 85.7 per cent of the 14 cases in which patients had two or more instructional treatments and in 68 per cent of the 25 cases in which patients followed the hospital routine. If we total the last two sets of data, we have 39 cases of rheumatoid arthritis, in all of which two or more treatments were given and in 74.4 per cent of which benefit resulted from treatment at home. In 61 (63.5 per cent) of the total of 96 cases of rheumatoid arthritis, benefit resulted from treatment at home.

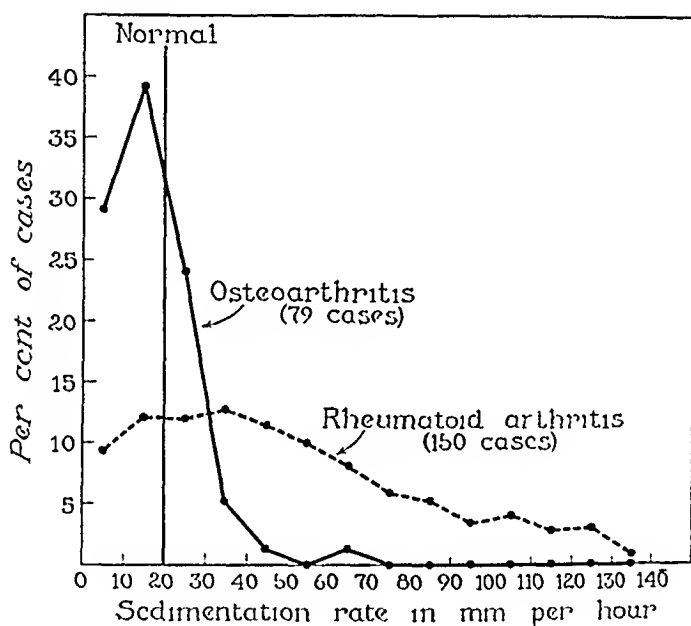
Likewise, of the cases of osteoarthritis, benefit was obtained in 62.3 per cent of the 69 cases in which patients had received just one instructional treatment and in 69.2 per cent of the 13 cases in which patients had received two or more treatments, while in the total of 52 (63.4 per cent) of the 82 cases of osteoarthritis in which patients were given instructional treatments, benefit was derived from home treatment.

The consultants in the Section on Physical Therapy have always been reluctant to give instruction without any demonstration treatment, but in 1 case of rheumatoid arthritis and in 2 cases of osteoarthritis this was done. In 2 of these 3 cases, incidentally, the patients stopped their treatment for reasons other than improvement.

A by-product of this study is observations on the sedimentation rates of the erythrocytes in 150 cases of rheumatoid arthritis and in 79 cases of osteoarthritis.



We were able to include more cases of rheumatoid arthritis here than in the main study, since we could include those cases in which questionnaires were sent and records were analyzed but in which no response was obtained. The sedimentation rates obtained in these cases are given in table 6 and in the figure. With 19 mm per hour taken as the upper limit of normal, the sedimentation rates were more rapid than normal in about four fifths of the cases of rheumatoid arthritis but in only about a third of the cases of osteoarthritis. Whereas the sedimentation rates were more than 40 mm per hour in only 2.5 per cent of the cases of osteoarthritis, they were more than 40 mm per hour in more than half of the cases of rheumatoid arthritis. In the figure these same facts are set forth strikingly, the precipitous drop that occurs in the curve for the cases of osteoarthritis as soon as the rates are beyond the normal range should be compared with the slow steady drop of the curve for the cases of rheumatoid arthritis.



Sedimentation rates in cases of osteoarthritis and of rheumatoid arthritis. The line marked normal is drawn at the lower limit of the abnormally increased rates.

#### COMMENT

The most significant fact obtained from this study is that in 92.7 per cent of cases arthritic patients carried out physical therapy in the home as prescribed and outlined for them. Furthermore, the facts that in 64.7 per cent of cases the patients were continuing the treatments for three months or longer after dismissal from the clinic and that in 26.6 per cent of cases they were still carrying on at home a year after dismissal appeared equally interesting. These observations indicate that if physical measures are prescribed individually and in some detail, they will be followed in the home by the patient as definitely and carefully as any other form of prescribed treatment. It might be stressed that this large percentage of patients continued their regimen, in most cases, under the direction of their physician in their home locality without making any return visits to the clinic for further instruction or encouragement and without supplementary professional physical therapy.

As to the subjective response of the patients in an evaluation of benefit received, we realize that this is not proof of "cure" or even of benefit for arthritis by the

home use of physical measures. Certainly many, in fact most, of these patients were placed on a complete therapeutic regimen, and credit is not being claimed for physical therapy as the only beneficial part of the program. Nevertheless, the patient's ideas as to whether the prescribed physical measures were of benefit are valuable, because, after all, patients come to us as physicians for help. If patients as a large group state that the prescribed program of home-applied physical therapy definitely gives them benefit, then until more specific remedies can be prescribed for the different types of arthritis, we are certainly encouraged to think that it is worth while to continue prescribing home physical therapy which in 40.4 per cent of cases our patients enthusiastically say helped them and which in 79.8 per cent of cases our patients think gave them some benefit and relief.

From the more detailed analysis we can draw one other conclusion which was more or less anticipated. The patients who had rheumatoid arthritis in general were more enthusiastic about the amount of benefit they received than were those who had osteoarthritis. Yet if we compare the simpler criteria of help received by the treatment by comparing the totals in tables 4 and 5, we see that in comparable series of cases of rheumatoid arthritis and of osteoarthritis, the percentages were almost identical, 63.4 and 63.5, for cases in which patients either were still continuing the treatments after a year or had stopped because of improvement. This indicates that although the patients who had rheumatoid arthritis responded more enthusiastically, as we would expect, nevertheless, as a whole, in about the same percentage of cases the patients who had osteoarthritis and those who had rheumatoid arthritis failed to carry on because of lack of some measure of improvement or benefit.

The other really worth while conclusion from tables 4 and 5 is that it is certainly of importance, wherever possible, for patients to take more than one instructional treatment. Of the group of cases of rheumatoid arthritis, there was more improvement in those cases in which patients took two or more instructional treatments than in those cases in which patients had only one instructional treatment. At first glance there also seemed to be more improvement in the former cases than in those in which patients were given the more strenuous routine of twenty instructional treatments at the hospital. This, however, is undoubtedly due to the fact that as a group the patients for whom the hospital course was advised were much sicker. In spite of this, we see that in more cases (68 per cent as compared with 56.1 per cent) those patients who took the hospital routine of treatments did well than did their less seriously afflicted fellow patients who took only one instructional treatment. If all cases in which the patients with rheumatoid arthritis who took two or more instructional treatments are considered, we see at a glance that these patients had a significant advantage over patients who took only one instructional treatment (improvement in 74.4 per cent of cases as compared with 56.1 per cent).

In cases of osteoarthritis a similar difference in percentage occurs, though not as great, there was improvement in 69.2 per cent of the cases in which patients took more than one instructional treatment as compared to 62.3 per cent of the cases in which patients had only the one. This only means that in osteoarthritis it is not as important, though still of some possible value, to encourage the patient to take an extra instructional treatment or two.

The physical measures advised for home use are all simple and may be adapted to the most meager facilities, yet they must be learned accurately and carried out precisely if they are to give maximal benefit. The extra instructional treatment or two seems to impress on the patient to a greater extent just what and how he is to carry on at home. Many patients think they can just read instructions and follow

them Our experience indicates that when, in addition to printed instructions, a demonstration treatment, or better two, is given the patient learns more readily just how he should carry out the prescribed measures He is then more likely to continue with the treatments and to derive the desired benefit When a patient does take a couple of treatments weekly from a skilled technician, as is advised whenever possible, it is important that he be warned that any such program is entirely inadequate if the home part of the routine between professional treatments is neglected

Table 6 is included merely as an interesting summary of the sedimentation rate of the erythrocytes in comparable series of cases of rheumatoid arthritis and of osteoarthritis In general, the distribution of the sedimentation rates as we found them in rheumatoid arthritis and in osteoarthritis was about the same as those already reported in the literature<sup>2</sup> The rheumatoid arthritis was of all stages, and this accounts for the fact that sedimentation rates were within the normal range in 21.3 per cent of the cases In 68.3 per cent of the cases of osteoarthritis the sedimentation rate was within the normal range, and in only 2 cases was the sedimentation rate more than 40 mm per hour The sedimentation rate is not a specific test and is elevated under many circumstances, and, as would be expected, we found that associated and coincidental processes accounted for many of the sedimentation rates that were more than normal in the cases of osteoarthritis

#### SUMMARY

A follow-up study was made in 218 cases of all types of arthritis in which home physical therapy was prescribed Of these 218 cases, patients in 92.7 per cent carried out the prescribed treatments at home and in 64.7 per cent continued the treatments for three months or longer Patients who received more than one instructional treatment were more likely to carry on the regimen at home with improvement than were those who had only one

In approximately 4 out of 5 cases of arthritis patients thought they were benefited by the use of home physical measures, and in 2 out of 5 they were definitely enthusiastic in their replies In general, patients who had rheumatoid arthritis were more enthusiastic about the benefit received than were those who had osteoarthritis, but on rough analysis the beneficial results obtained by both groups were comparable

Data on the sedimentation rates in 150 cases of rheumatoid arthritis and in 79 cases of osteoarthritis were presented

#### CONCLUSIONS

To be effective in the therapeutic program of a case of arthritis, physical therapy should be carried on daily over long periods of time in the home Each patient should be prescribed for individually by a physician and should be instructed in one or more demonstration treatments just how he is to carry on at home When physical therapy is prescribed with proper care for arthritic patients and the patients are instructed with sufficient detail, a gratifying number of them continue the treatments at home and feel that they are benefited in so doing

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2 Slocumb, C. H. Differential Diagnosis of Periarticular Fibrositis and Arthritis, *J. Lab. & Clin. Med.* 22: 56-63 (Oct.) 1936 Hench<sup>1a</sup>

# EFFECT OF EXERCISE ON BLOOD PYRUVIC ACID

OBSERVATIONS ON TRAINED AND UNTRAINED NORMAL SUBJECTS  
AND ON PATIENTS WITH HEART DISEASE AND  
WITH HYPERTENSION

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An increase of lactic acid in the blood and tissues following exercise is one of the classic observations in physiology. Since this discovery an extensive literature has accumulated on changes in lactic acid as related to work, training and fatigue. More recently Dill and his group<sup>1</sup> have suggested that it be employed as an index of cardiovascular fitness. However, it is now the considered opinion of most biochemists<sup>2</sup> that pyruvic acid, and not lactic acid, is the core of the carbohydrate metabolism of tissues. In the breakdown of dextrose by the tissues all reactions appear to revolve around pyruvic acid as the pivotal point. Further interest has been attached to pyruvic acid because of Peters'<sup>3</sup> discovery that the presence of vitamin B<sub>1</sub> is necessary for its oxidation. This displacement of lactic acid in the scheme of the carbohydrate metabolism of tissues by pyruvic acid led to the formulation of this work.

## METHOD AND MATERIAL

A standard exercise of fifty ascents and descents in one hundred seconds over a two step contrivance,<sup>4</sup> with the blood level of pyruvate determined while the subject was resting and ten and sixty minutes after the exercises, was performed by 11 wrestlers and track men aged 18 to 21 from the University of Chicago, 10 persons aged 19 to 54 engaged in sedentary occupations, 10 patients aged 21 to 48 of functional classes II and III with cardiac disease and enlargement and 9 hypertensive patients aged 31 to 51 of functional class I without cardiac enlargement or detectable renal involvement but with systolic blood pressures exceeding 200 mm of mercury.

Blood pyruvate was analyzed by Friedemann's modification<sup>5</sup> of Lu's method<sup>6</sup>. Preliminary investigation revealed the ten and the sixty minute period to be optimum for study.<sup>7</sup>

From the Department of Medicine of the University of Chicago

This investigation was aided by a fellowship grant from the Jessie Horton Koessler Fund of the Institute of Medicine, Chicago, and by a grant from the Douglas Smith Fund of the University of Chicago.

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Cori, C. F., and Cori, G. T. Carbohydrate Metabolism, *ibid* **10** 151, 1941.

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6 Lu, G. D. Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B<sub>1</sub> Deficient States. I. A Rapid Specific and Sensitive Method for the Estimation of Blood Pyruvate, *Biochem J* **33** 249 (Feb) 1939.

7 These time intervals were selected at the suggestion of Dr. Theodore E. Friedemann, of the Abbott Foundation for Medical Research, Northwestern University (personal communication).

The ten minute changes in blood pyruvate of the untrained subjects and of the patients with heart disease and with hypertension were found to be statistically significant. None of the groups, with the exception of the patients with heart disease, could be shown to have statistically significant sixty minute changes. Fisher's rule<sup>9</sup> stipulates that a critical ratio of 2 represents statistical significance. The calculated critical ratio of the sixty minute changes of the patients with heart disease was 1.42, and this is close enough to 2 to place the sixty minute changes of the patients with cardiac disease in the realm of "practical" significance.

In the untrained group the subjects were all closely alike in daily physical activity, but there was a purposeful wide age variation to match the age range of the patients with heart disease and with hypertension. That the ten minute changes were significant would indicate that age was not a modifying factor in these changes. The ten and sixty minute changes of the other groups were similarly not influenced by age.

In the patients with heart disease and with hypertension there were individual differences based on such variables as duration, type and magnitude of symptoms, functional capacity, cardiac enlargement, degree of cardiac damage and stress, number of failures, and lability of blood pressure. It is usually impossible to select a group of patients who are standardized on all the variables of clinical experimentation. In the main these variables were related to the changes in blood pyruvate. The patients of functional class III with heart disease (table 3) had the highest sixty minute levels, and the duration of the cardiac symptoms and the number of cardiac failures of each patient tended to be expressed by the greater ten and sixty minute changes. This is an encouragement to further investigation, as there is need for precise measurement of the functional capacity of a patient with cardiovascular disease in terms of the actual chemical processes that the body utilizes to perform work.

Pulse recovery time following exercise did not seem to correlate with the changes in blood pyruvate except for the hypertensive patients whose ten minute changes and pulse recovery times were of the same magnitude. The group of patients with heart disease was the only one that showed a similar trend in the ten and the sixty minute changes in blood pyruvate for each subject, a high ten minute increase in this group seemed to correspond to a high sixty minute increase.

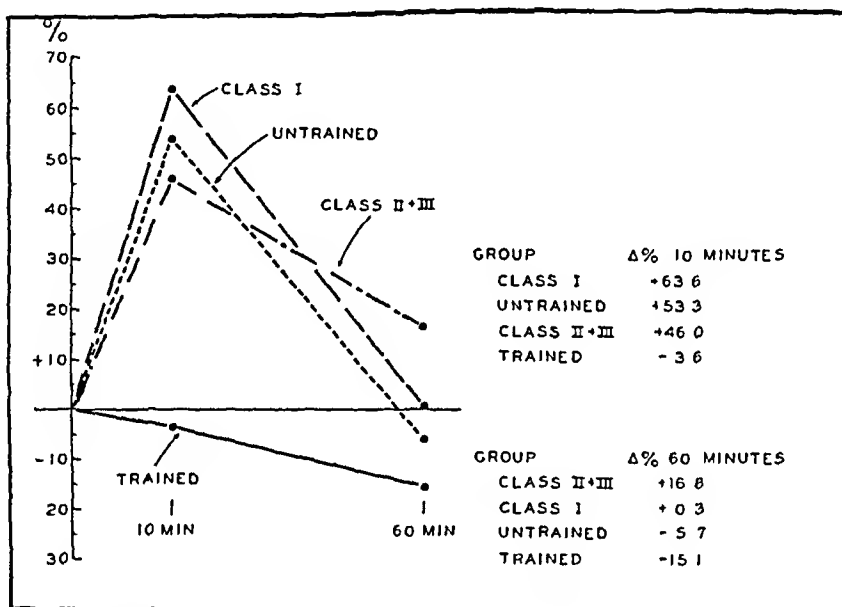
All the hypertensive patients led sedentary lives except 1 truck driver and 1 maintenance man. The former daily lifted heavy objects, while the latter walked about 16 miles (26 kilometers) daily in his work. It is of interest that even though these men were in some form of training, their changes in blood pyruvate were in no way similar to those of the more rigidly trained subjects. The truck driver who daily did some heavy work had a ten minute rise of +64 per cent and a sixty minute change of +32 per cent, the latter value being the highest in the group. No explanation for this is available.

*Comparisons of Group Means (figure)*—The ten minute values of the trained group contrasted with those of the other groups, and the initial "high normal" levels of some of the trained subjects indicate a change in the mechanism of carbohydrate utilization of trained persons as opposed to that of subjects in the other groups, whose hearts *only* are working overtime. This observation suggests a clue to the complex chemical changes involved in "training" and "compensation." These ten minute changes could also conceivably be used as a practical criterion of physical fitness.

<sup>9</sup> Dunn, H. L. Application of Statistical Methods in Physiology, *Physiol Rev* 9:275 (April) 1929.

By doing some calculations made possible by what is known about the work of the heart, it can be shown that the heart of a hypertensive person probably does more work in twenty-four hours than does the heart of a trained man doing his usual exercise. From this we might expect the hypertensive person to be in some form of training. But the changes in blood pyruvate of the two are notably different. It would appear that the use of body muscles is necessary to achieve the state of training. Thus the old thought that patients with heart disease should exercise up to their respective limits may not have been too far fetched.

The mean sixty minute change in blood pyruvate of the trained subjects was  $-15.1$  per cent of the resting levels, that of the untrained subjects  $+5.7$  per cent, that of the hypertensive subjects  $0$  and that of the subjects with cardiac disease  $+16.8$  per cent. The order of progression from negative to positive sixty minute changes is more or less in keeping with the cardiac function of each group. These sixty minute changes also suggest a possible index of cardiovascular fitness, and further, this test could presumably be used to follow the course of a patient



Mean changes in blood pyruvate after moderate exercise

with heart disease. This is further supported by the previously mentioned fact that patients of functional class III with heart disease with the poorest cardiac function (with 1 exception) had the highest positive sixty minute changes. This also fits in with a recent paper in which I<sup>10</sup> reported high blood levels of pyruvate occurring in patients with heart failure.

*Comparisons of Lactate*—The literature of changes in blood level of lactic acid following exercise indicates that lactate both in trained and in untrained subjects increases only after strenuous exercise and not after moderate exercise<sup>11</sup>. In this study blood pyruvate increased after only light to moderate exercise as much as 131 per cent. Thus, blood pyruvate is available for study as a chemical indicator of physiologic changes related to exercise in untrained subjects on whom severe exercise would be a hardship and in patients who are not capable of undertaking the severe exercise that determination of blood lactate requires.

10 Yanof, Z. A. Blood Pyruvic Acid in Heart Disease, Arch Int Med **69** 1005 (June) 1942

11 Dill, D. B. The Economy of Muscular Exercise Physiol Rev **16** 263 (April) 1936

In the trained subjects the mean ten and sixty minute percentage changes were apparently not significant and thus are comparable to the stability of blood lactate after moderate exercise. However, there are no reported changes in lactate that are comparable to the individual negative sixty minute changes in blood pyruvate of the trained group. Blood levels of lactate during rest apparently do not increase with training and so are not comparable to the 4 elevated levels of pyruvate during rest encountered in this study.

The increase of pyruvate in the blood after both moderate and severe<sup>12</sup> exercise, and the failure of lactate to increase in the blood except after exhausting exercise indicate that pyruvate is an important and obligatory intermediate (if not the principal) metabolite in the chemical mechanism of any muscular contraction, with lactate coming into play as a secondary auxiliary system when the anoxic conditions of heavy exercise are present. This fits in with the present day concept of the central place that pyruvic acid occupies in the carbohydrate metabolism of tissue, and is further inferential support of the foregoing observations on the greater sensitivity of pyruvate level in exercise physiology.

Analysis of blood pyruvate is also more accurately and more easily accomplished than analysis of lactate.

#### CONCLUSIONS

Ten minutes after moderate exercise a group of trained subjects had no significant change in blood level of pyruvate, while untrained subjects and patients with heart disease and with hypertension had in contrast marked rises of pyruvate in the blood.

The sixty minute changes of the group of patients with heart disease were significantly high and were proportional to functional capacity.

Blood pyruvate measurably increases after moderate exercise in untrained subjects and in patients with cardiovascular disease, while lactate does not, and so estimations of pyruvate can be utilized in the study of cardiovascular fitness of untrained subjects and patients who are not capable of undertaking the strenuous exercise that measurement of blood lactate requires.

Dr Emmet B. Bay offered guidance and criticism.

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<sup>12</sup> P. E. Johnson and H. T. Edwards (Lactate and Pyruvate in Blood and Urine After Exercise, *J. Biol. Chem.* **118** 427 [April] 1937) and T. E. Friedemann and C. J. Barborika (The Significance of the Ratio of Lactic to Pyruvic Acid in the Blood After Exercise, *ibid.* **141** 993 [Dec.] 1941) have reported increases in blood pyruvate as accompanying increases in blood lactate in trained subjects after severe exercise.

# LIMITATIONS OF THE ERYTHROCYTE SEDIMENTATION TEST IN TUBERCULOSIS

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Since the introduction of the erythrocyte sedimentation test into clinical practice numerous publications have dealt with its value in the diagnosis, prognosis and treatment of tuberculosis. The overwhelming majority of articles reflect the following convictions: 1 It is a reliable gage for the detection of active pulmonary tuberculosis. 2 The sedimentation rate of erythrocytes is directly proportionate to the extent of tuberculosis. 3 The test conforms rather snugly to the underlying pathologic process, being more rapid in association with the predominantly exudative type of lesion than in the case of productive or fibrosing tuberculosis. 4 An increased rate of erythrocyte sedimentation is of direct prognostic value and a sensitive signal of an oncoming spread of the disease. 5 In cases of pulmonary tuberculosis in which collapse therapy is instituted the test is a competent index of improvement which may not be detectable by other clinical means.

For the purpose of ascertaining the clinical value of this test we have analyzed the records of 2,640 tuberculous patients who were under observation at this sanatorium during the past four and a half years. We were prompted to make this study by finding definite discrepancies between the results of the sedimentation test and other laboratory and clinical data used as indicators of the activity of the disease. Roentgenologically demonstrable active tuberculous lesions and gastric contents or sputum positive for tubercle bacilli together with a normal sedimentation rate were encountered in infants, children, adolescents and adults. In some patients whose disease was discovered through health surveys normal sedimentation velocity was encountered in the presence of active pulmonary tuberculosis with sputum positive for tubercle bacilli. We have found also that as an indicator for the onset of the reinfection type of tuberculosis in nurses exposed to tuberculous patients a normal erythrocyte sedimentation rate is of questionable value and that it does not compare favorably with serial roentgenograms of the chest. Therefore, in view of the unhesitating reliance on this procedure by many physicians who are seeing tuberculous patients, we thought it justifiable to call attention to our observations.

Extensive clinical and experimental studies have brought out various theories concerning changes in the sedimentation rate. Fahraeus<sup>1</sup> expressed the opinion that they are due to qualitative changes in the serum globulins, particularly in fibrinogen. Ernstene<sup>2</sup> demonstrated that variations in the amount of fibrinogen and not in its quality are the decisive factors. Hille<sup>3</sup> expressed the belief that

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1 Fahraeus, R. Suspension Stability of Blood, *Acta med Scandinav* **55** 3, 1921.

2 Ernstene, C. Erythrocyte Sedimentation, Plasma Fibrinogen and Leukocytosis as Indices of Rheumatic Infection, *Am J M Sc* **153** 12, 1930.

3 Hille, G. Colloid Stability and Sedimentation Test in Infants, *Monatschr f Kinderh* **28** 137, 1924.



besides the colloid balance of the blood the number of red cells and the amount of hemoglobin are of significance in this respect. Early investigators suggested that the sedimentation rate is influenced by the difference in the electrical potential between the negatively charged red cells and the positively charged proteins of the plasma, greater negative charge of the red cells was encountered in serum albumin than in serum globulin or in serum fibrinogen. Bernou<sup>4</sup> regarded the viscosity of the whole blood and not that of the plasma alone as the chief determining factor. Accordingly, an increase in the volume of the individual blood corpuscles, which increases the viscosity, causes a retardation of the settling, while an increase in the globulin, which forms large molecules at the expense of the albumin, reduces viscosity and leads to a rapid sedimentation of the red cells. Cutler and his associates<sup>5</sup> made a critical appraisal of the role anemia plays in the sedimentation of erythrocytes. They came to the conclusion that anemia has little to do with it and that increased sedimentation is caused by the erythrocytes forming large aggregates, or rouleaux. They stated that the formation of aggregates of erythrocytes is the function of the plasma and is specific for any given plasma, the latter is little influenced by the size, shape or number of erythrocytes in suspension.

In the evaluation of this test one also has to keep in mind that a number of incidental factors influence its outcome. The settling of the red cells is faster in women than in men<sup>6</sup>, also, Bertrand and Rousseaux<sup>7</sup> reported that there are rhythmic variations in the sedimentation rate during the phases of the menstrual cycle. There is a premenstrual and menstrual increase induced by an increase in the amount of fibrinogen. The rate is increased during pregnancy<sup>8</sup> and in old age<sup>9</sup>. The possible effect of the endocrine glands was also investigated. Runnstrom and Schow<sup>10</sup> found that accelerated settling occurred in experimental animals after thyroidectomy. It was demonstrated by Lockett<sup>11</sup> that exercise is followed by an accelerated settling, this effect may persist for some time. He also observed that the rate is decreased during digestion, reaching its slowest progress in one to one and a half hours after intake of food. A correlation between the carbon dioxide content of the venous blood and the sedimentation rate was noted by Freeman<sup>12</sup>. Pinner and his associates<sup>13</sup> emphasized the fact that rather wide variations occur from day to day in normal persons. Hoverson and Peterson<sup>14</sup> offered an explana-

4 Bernou, M. Red-Cell Sedimentation and Blood Viscosity, *Rev de la tuberc* **2** 152, 1936

5 Cutler, J. W., Park, F. R., and Herr, B. S. Influence of Anemia on Blood Sedimentation, *Am J M Sc* **195** 734, 1938

6 Fahraeus, R. Suspension Stability of Blood, *Physiol Rev* **9** 241, 1929

7 Bertrand, P., and Rousseaux, R. Contribution to the Study of the Sedimentation Rate, *Rev franç d'endocrinol* **10** 362, 1932

8 Bland, P. B., Goldstein, L., and First, A. Sedimentation Test in Pregnancy and Puerperium. Study of Five Hundred and Forty Patients, *Surg, Gynec & Obst* **50** 429, 1930

9 Lasch, F. Study of the Cause of Acceleration of the Sedimentation Rate in the Aged, *Wien Arch f inn Med* **22** 155, 1931

10 Runnstrom, J., and Schow, S. A., cited by van Antwerp, L. D. Repeated Sedimentation Tests, *Am J Dis Child* **48** 814 (Oct) 1934

11 Lockett, M. F. Study of Certain Factors Affecting the Sedimentation Rate, *Brit J Tuberc* **31** 31, 1937

12 Freeman, H. Sedimentation Rate of Blood in Schizophrenia, *Arch Neurol & Psychiat* **30** 1298 (Dec) 1933

13 Pinner, M., Knowlton, K., and Kelly, R. G. Sedimentation Rate of Erythrocytes. Its Relation to Fibrin Value and Cholesterol Content and Its Application in Tuberculosis, *Arch Path* **5** 810 (May) 1928

14 Hoverson, E. T., and Peterson, W. F. Meteorologic Effects on the Sedimentation Rate of the Erythrocytes. *Am J M Sc* **188** 455, 1934

tion for this observation. They postulated that meteorologic conditions induce demonstrable changes in the human body which may be measured by chemical examination of the blood and that these chemical alterations in the blood account for the daily variations in the erythrocyte sedimentation rate.

Experimental work on tuberculous animals revealed that both immunity and the allergic status may have some bearing on the outcome of the test. Dwelshawers<sup>15</sup> found that the sedimentation rate remained normal in rabbits which were first inoculated with an avirulent strain of tubercle bacilli and inoculated subsequently with virulent bovine tubercle bacilli, while in nonimmunized controls the sedimentation rate was rapid. On the other hand, Freund and Frank<sup>16</sup> demonstrated that the injection of old tuberculin into tuberculous rabbits was followed by a considerably increased sedimentation rate.

There is no doubt that the erythrocyte sedimentation rate is subject to the same physical laws that apply to particles suspended in fluid medium, as expressed by Stokes's formula  $V = \frac{2}{9} g \frac{S - S_1}{u} r^2$ , in which  $V$  = the velocity of fall,  $g$  = the gravitation constant,  $S$  = the specific gravity of the red blood cells,  $S_1$  = the specific gravity of the blood plasma,  $u$  = the absolute viscosity of the plasma and  $r$  = the radius of the rouleaux, or aggregates of erythrocytes. According to this formula, the sedimentation rate is directly proportional to the square of the radius of the red cell aggregates and inversely proportional to the viscosity of the plasma.

It must be kept in mind that certain factors which influence the chemical activity of the body in some particular manner—in health or during the course of tuberculosis—may play a part in the outcome of the sedimentation test. Therefore, no correct interpretation of the result is possible unless due consideration is given to the potential effect of these factors. If this is so, it is evident that variations in the erythrocyte sedimentation rate in a tuberculous person are bound to reflect the influences of factors that may have nothing to do with the type, extent and course of the tuberculous process.

The limitations of the erythrocyte sedimentation test in tuberculosis are best illustrated by brief summaries of representative cases.

#### REPORT OF SIX CASES

*CASE 1—Active primary tuberculosis in a white infant with a normal erythrocyte sedimentation rate*

A. M., an infant white girl aged 8 months, was admitted to the sanatorium with the diagnosis of an active primary tuberculous infection, with an involvement of the hilar lymph nodes and the perihilar pulmonary parenchyma. The cutaneous reaction to tuberculin was strongly positive. Aspirated gastric contents were positive for tubercle bacilli on culture, and at the same time the erythrocyte sedimentation rate was normal. Because of the positive culture she was treated at the sanatorium for fifteen months, recovery was complete.

*CASE 2—Active pulmonary tuberculosis in an adolescent white girl with a normal erythrocyte sedimentation rate*

V. J., a white girl aged 14, was admitted to the sanatorium with complaints of cough, thoracic pain, loss of strength and night sweats. A roentgenogram of the chest showed a parenchymal infiltration in the apical and the subapical area of the left lung. Her temperature was subfebrile occasionally during the first two months of her stay. Aspirated gastric contents were positive for tubercle bacilli on culture and on inoculation into guinea pigs and her erythrocyte sedimentation rate was normal on admission.

<sup>15</sup> Dwelshawers, F. Blood Sedimentation and Antibody Response in Rabbits, *Compt rend Soc de biol* **123** 549, 1936.

<sup>16</sup> Freund, J., and Frank, D. E. Sedimentation Rate of Red Blood Cells in Tuberculous Rabbits Injected with Tuberculin, *J Immunol* **24** 247, 1933.

*CASE 3—Toxic symptoms in pulmonary tuberculosis in a white woman with a normal erythrocyte sedimentation rate*

G S, a white woman aged 39, was admitted with moderately advanced active pulmonary tuberculosis. She complained of chills, fever, night sweats, anorexia, loss of weight, weakness and fatigue. Physical examination and a roentgenogram showed active disease in the upper one third of both lungs. The sputum was positive for tubercle bacilli on culture, and the erythrocyte sedimentation rate was normal.

*CASE 4—Caseous pulmonary tuberculosis in a Negro with a normal erythrocyte sedimentation rate*

B P, a Negro aged 48, began to cough and raise greenish yellow mucoid sputum nine months before admission, he expectorated about 1 fluidounce (30 cc) of sputum a day. He complained of moderate cough and loss of strength and weight. A roentgenogram showed a caseous infiltration in the right lung, extending to the third rib anteriorly and to the sixth dorsal spine posteriorly. On admission his sputum was negative for tubercle bacilli, but aspirated gastric contents were positive for tubercle bacilli on culture and on inoculation into guinea pigs. At the same time his erythrocyte sedimentation rate was normal.

*CASE 5—Pulmonary tuberculosis with honeycomb cavitation in a white woman with a normal erythrocyte sedimentation rate*

E D, a white woman aged 33, was admitted to the sanatorium with the complaints of persistent cough and loss of weight of four months' duration, also blood streaking of sputum and dyspnea. The results of physical examination indicated an active tuberculous process in the upper third of the left lung. A roentgenogram showed a heavy fibrocaceous infiltration in the middle third and the subapical region of the left lung with honeycombing. The sputum was classed as II on the Gaffky scale examination, the erythrocyte sedimentation rate was normal.

*CASE 6—Far advanced pulmonary tuberculosis with a large open cavity in a white man with a normal erythrocyte sedimentation rate*

J S, a white man aged 55, was admitted with the complaints of moderate cough, expectoration and dyspnea. Numerous moist rales were heard over the upper third of the right lung anteriorly and throughout posteriorly, also over the apical area of the left lung. A roentgenogram revealed a bilateral fibrocaceous infiltration largely confined to the upper half of each lung, there was a cavity measuring 45 by 70 mm in the upper lobe of the right lung. His sputum was positive for tubercle bacilli on direct examination, and the erythrocyte sedimentation rate was normal.

#### COMMENT

A normal sedimentation rate may occur in the presence of considerable destruction of tissue, honeycomb cavitation, a large solitary excavation or multiple cavities. We have noted during the course of various measures of collapse therapy that in some of our patients the originally accelerated sedimentation rate returned to normal shortly after the institution of treatment, although simultaneously clinical data showed that pulmonary cavities remained open and the disease continued to be active.

Furthermore, we have encountered normal sedimentation velocity in a patient with bacteriologically proved tuberculous empyema and in patients with pulmonary tuberculosis and the following tuberculous complications: cervical adenitis, arthritis, bronchiectasis, renal tuberculosis, tuberculous pleurisy with effusion, tuberculoma of the larynx and lupus vulgaris. Normal rates were recorded for a patient with active pulmonary tuberculosis superimposed on silicosis and a patient with diabetes mellitus complicated by pulmonary tuberculosis. Also, we have encountered normal sedimentation of erythrocytes in a patient with draining tuberculous cervical adenitis, tuberculous tenosynovitis, pleurisy with effusion and tuberculosis of the bone and in a patient with bilateral renal tuberculosis.

Of the 2,640 tuberculous patients included in this study, a normal sedimentation rate and active disease were found simultaneously in 212, or 8 per cent. Of these patients, 206 had pulmonary tuberculosis and 6 had extrapulmonary tuberculosis.

Of the patients with pulmonary tuberculosis 13 were not classified as to the stage of their illness because of the concurrent measures of collapse therapy applied to the lungs. The remaining 193 come under the following classification of the National Tuberculosis Association: minimal infection 18, or 9.3 per cent, moderately advanced infection 95, or 49.2 per cent, far advanced infection 51, or 26.4 per cent, and active primary infection 29, or 15 per cent.

From the review of the illustrative cases and other data presented in this paper one is justified in concluding that the result of the erythrocyte sedimentation test does not reflect the true pathologic status of tuberculosis. Consequently, this test cannot be considered an accurate or reliable index for the management of a tuberculous patient, that is, for prescribing necessary rest in bed or permissible exercise, for planning collapse therapy or for making the periodic follow-up examinations of patients with "apparently arrested" tuberculosis.

#### SUMMARY

A study of the erythrocyte sedimentation rate of 2,640 tuberculous patients observed during the past four and a half years revealed that 8 per cent of them had a normal sinking velocity.

Simultaneous occurrence of active tuberculosis and a normal sedimentation rate was observed in all age groups and in patients with primary infection as well as in ones with a reinfection type of disease.

The erythrocyte sedimentation rate does not parallel the type and the extent of tuberculosis. Normal rates were encountered in association with minimal, moderately advanced and far advanced infection, with productive and with exudative pulmonary tuberculosis and with solitary or multiple cavities. The size of the pulmonary cavities varied from honeycombing to cavities 45 mm by 70 mm in diameter.

Sputum positive for tubercle bacilli examined directly or after homogenization or aspirated gastric contents positive for these organisms (on culture or on inoculation into guinea pigs) were encountered in association with a normal sedimentation rate.

The type and length of a regimen based on rest in bed cannot be gaged by the sedimentation test, because the rate may return to normal shortly after the beginning of treatment or much earlier than the healing of the parenchymal process takes place.

The eligibility of a patient to become ambulatory and undergo pneumothorax treatment should not be decided on the basis of a normal sedimentation rate unless the results of other procedures are corroborative, including aspiration of gastric contents that are repeatedly negative for tubercle bacilli on culture or on inoculation into guinea pigs.

During the course of various measures of collapse therapy the sedimentation rate may return to normal while cavities remain open and the tuberculous process is still active.

#### CONCLUSIONS

1. It is our impression that the clinical value of the erythrocyte sedimentation test in tuberculosis is greatly overestimated.

2. Our observations indicate that it has considerable limitation, therefore, it should not be used as an independent index in the management of tuberculous patients.

# ESTROGEN, DIABETES AND THE MENOPAUSE

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In the several years since the work of Evans and co-workers<sup>1</sup> and of Houssay and co-workers<sup>2</sup> the relationship of the anterior lobe of the pituitary gland to carbohydrate metabolism has been rather firmly established. More recently Young<sup>3</sup> has been able to produce permanent diabetes by the use of potent extracts of the anterior lobe of the pituitary gland prepared at freezing temperatures. The pancreas of animals with such diabetes was found to show an atrophy of the islands of Langerhans and by actual assay very little or no insulin.

The menopause is associated with hyperactivity of the anterior lobe of the pituitary gland. Thus any of its chemical products or biologic functions may be increased. If among these products the "diabetogenic" factor is increased it can produce diabetes or aggravate an existing diabetes either by its antagonistic action to insulin or, more fundamentally, by its effect functionally or even anatomically in producing hydropic and hyaline degeneration or atrophy of the islands of Langerhans.

During the menopause the subjective and objective vasomotor disturbances and the increased amount of gonadotropic hormone in the blood and urine are evidences of the overactivity of the anterior lobe of the hypophysis. Such overactivity seems to be in inverse proportion to the atrophy and diminished function of the ovaries and the consequent decrease of available estrogenic follicular hormone. The overfunctioning anterior lobe of the pituitary gland then secretes an overabundance of all its hormones in addition to the gonadotropic, and one of these is the "diabetogenic" hormone.

Tuttle<sup>4</sup> observed that the onset of diabetes coincided with that of the menopause in 38 of 72 diabetic women. Joslin<sup>5</sup> attributed the preponderance of diabetes in middle-aged women to the obesity so frequently occurring at the menopause.

From the Diabetic Clinic of Lebanon Hospital

The cases reported were presented at meetings of the Society of Alumni of Lebanon Hospital and the North Bronx Medical Society.

1 Evans, H M, Meyer, K, Simpson, M E, and Reichert, F L. Disturbance of Carbohydrate Metabolism in Normal Dogs Injected with Hypophyseal Growth Hormone, *Proc Soc Exper Biol & Med* **29** 857-858 (April) 1932.

2 Houssay, B A, and Biasotti, A. Pankreasdiabetes und Hypophyse beim Hund, *Arch f d ges Physiol* **227** 664-684 (June 22) 1931, Carbohydrate Metabolism and Diabetes, *Endocrinology* **15** 511-523 (Nov-Dec) 1931, Diabetes as a Disturbance of Endocrine Regulation, *Am J M Sc* **193** 581-606 (May) 1937. Houssay, B A. The Hypophysis and Metabolism, *New England J Med* **214** 961-971 (May 14) 1936. Houssay, B A, and Magenta, M A. Sensibilidad en los perros hipofisoprivos a la insulina, *Rev Asoc med argent* **37** 389-406, 1924.

3 Young, F G. Studies in Fractionation of Diabetogenic Extracts of the Anterior Pituitary Gland, *Biochem J* **32** 524-533 (March) 1938, The Anterior Pituitary Gland and Diabetes Mellitus, *New England J Med* **211** 635-646 (Oct 26) 1939, The Diabetogenic Action of Crude Anterior Pituitary Extracts, *Biochem J* **32** 513-523 (March) 1938, Anterior Pituitary Fractions and Carbohydrate Metabolism. The Preparation and Properties of Diabetogenic Extracts, *J Endocrinol* **1** 339-355 (Nov) 1939.

4 Tuttle, E. Diabetes Mellitus, *New York State J Med* **37** 636-642 (April 1) 1937.

5 Joslin, E P. An Appraisal of the Present Treatment of Diabetes, *J A M A* **97** 595-602 (Aug 29) 1931.

In general, diabetes has an onset at this age period even in the male, and this, together with the obesity at this time, may point to the pituitary factor as of importance in at least a proportion of cases of diabetes

Estrogen exerts an inhibitory effect on the anterior lobe of the pituitary gland. The administration of this substance, therefore, reduces pituitary hyperactivity during the menopause. This inhibitory effect has been demonstrated repeatedly and can be utilized as a means of assaying the proper dosage of estrogen. The dose is that which will result in disappearance of the gonadotropic factor from the urine. However, inhibition is not limited to the gonadotropic factor. Zondek<sup>6</sup> demonstrated inhibition of growth in infantile rats by administration of estrogen. He stated the belief that the effect of estrogen on the pituitary gland manifests itself first by reduction of its gonadotropic function and then by a reduction of its other functions.

Barnes, Regan and Nelson<sup>7</sup> have shown that the administration of amniotin to female dogs previously made diabetic by pancreatectomy renders them either non-diabetic or only mildly diabetic. Mazer and Israel<sup>8</sup> were among the first to report the ameliorating effect of estrogen on the diabetes, having noted this in 3 of their 51 menopausal patients treated with 2,000 rat units of estrogen as estradiol benzoate every four days. This amount of estrogen controlled the associated diabetes of these 3 women without the use of insulin, and any decrease in the dose of estrogen resulted in a return of hyperglycemia and glycosuria. Spiegelman<sup>9</sup> controlled the diabetes of 9 women by the administration of 10,000 international units of estrogen twice weekly. Goldman, Goldman and Kurzrock<sup>10</sup> noted the disappearance of the glycosuria and hyperglycemia of a diabetic patient who was 1 of 8 women treated with estrogen for the relief of menopausal symptoms and concomitant hyperthyroidism. Collens and co-workers<sup>11</sup> made an adverse report in a trial of amniotin on 7 persons with diabetes, 1 a male and all unselected as to menopause and age. They used a very small dose (100 to 400 rat units of estrogen). Gessler, Halsted and Stetson<sup>12</sup> selected for treatment 5 diabetic patients all past the menopause. In the first 2 diabetes began at the time of the menopause. In these patients there was an effect on the blood sugar. However, the complete results of the therapy were indefinite. These workers concluded that the conflicting results reported in the literature might be due to an inability to choose the proper type of diabetes for such treatment. Cantilo<sup>13</sup> obtained a 100 per cent good

6 Zondek, B. The Inhibitory Effect of Follicular Hormone on the Anterior Lobe of the Pituitary Gland, *Lancet* **1** 10-12 (Jan 4) 1936, Impairment of Anterior Pituitary Functions by Follicular Hormone, *ibid* **2** 842-847 (Oct 10) 1936, The Effect of Prolonged Administration of Estrogen, *J A M A* **114** 1850-1854 (May 11) 1940

7 Barnes, B. O., Regan, F. J., and Nelson, W. O. Improvement in Experimental Diabetes Following Administration of Amniotin, *J A M A* **101** 926-927 (Sept 16) 1933

8 Mazer, C., and Israel, S. L. Studies on the Optimal Dosage of Estrogen, *J A M A* **108** 164-169 (Jan 16) 1937

9 Spiegelman, N. R. Influence of Estrogen on the Insulin Requirement of the Diabetic, *Am J M Sc* **200** 228-234 (Aug) 1940

10 Goldman, S. F., Goldman, A., and Kurzrock, R. The Treatment of Menopausal Hyperthyroidism with Estrogenic Substance, *New York State J Med* **40** 1178-1184 (Aug 1) 1940

11 Collens, W. S., Slobodkin, S. G., Rosenblatt, S., and Boas, L. C. The Effect of Estrogenic Substance on Human Diabetes, *J A M A* **106** 678-682 (Feb 29) 1936

12 Gessler, C. J., Halsted, J. A., and Stetson, R. P. Effect of Estrogenic Substance on the Blood Sugar of Female Diabetics After the Menopause, *J Clin Investigation* **18** 715-722 (Nov) 1939

13 Cantilo, E. Successful Responses in Diabetes Mellitus of the Menopause Produced by the Antagonistic Action of Sex Hormones on Pituitary Activity, *Endocrinology* **28** 20-24 (Jan) 1941

response in 40 diabetic women in the menopause using estrogen and progesterone three times a week. He emphasizes the necessity of separating this "special type of climacteric diabetes." Our work was undertaken with this point in view.

In the diabetic clinic at Lebanon Hospital about 90 per cent of the patients are women who either have passed the menopause or are still suffering from its symptoms. Coincident with the menopause some patients show an aggravation of their diabetic state and therefore require more insulin. Such women were chosen for this study in an attempt to ascertain the relationship between the hyperactivity of the anterior lobe of the pituitary gland during the menopause and the aggravation of the diabetes and to determine whether the inhibitory effect of estrogen might have a favorable effect on the diabetes. For the same purpose we selected some patients who were observed to be diabetic at about the time of the onset of the menopause. To test the effect of estrogen when the menopause was not concerned, we included 2 patients who could not take insulin because of severe local reactions, presumably allergic, but who had no menopausal symptoms, to see what effect estrogen might have on diabetes in no way related to the menopause.

Thus there were four groups of patients: (1) those with a coincidental onset of diabetes and the menopause, (2) those whose diabetes was aggravated by the menopause, (3) those in whom the diabetes appeared long after the menopause and (4) those with no menopausal symptoms and presumptive allergic symptoms preventing the use of insulin.

#### REPORT OF CASES

##### 1. DIABETES MELLITUS DISCOVERED AT ABOUT THE TIME OF ONSET OF THE MENOPAUSE

**CASE 1**—Mrs. A. G., aged 50, came to the outpatient department of Lebanon Hospital because of pruritis vulvae, flushes and amenorrhea. Routine urinalysis revealed 2 per cent sugar, and the fasting blood sugar content was 360 mg per hundred cubic centimeters. She was given a diet of carbohydrate 100 Gm, protein 71 Gm and fat 70 Gm, with gradually increasing doses of protamine zinc insulin, but despite a final dose of 65 units daily she continued to show from 2 to 3 per cent sugar in her twenty-four hour specimen of urine. On Nov. 26, 1940, estrogen (2,000 rat units three times weekly)<sup>14</sup> was added to the regimen. The glycosuria rapidly cleared. The dose of insulin could then be rapidly reduced to 15 units daily. Eight months later the administration of estrogen was discontinued because of improvement in menopausal symptoms. The diabetic condition deteriorated, and the dose of insulin had to be increased to 35 units, although the diet was maintained as before. The results of two dextrose tolerance tests are here reproduced, one before the beginning of estrogen therapy and one before its cessation.

	Nov. 26, 1940		August 1941	
	Blood Sugar, Mg/100 Cc	Urinary Sugar, Percent-age	Blood Sugar, Mg/100 Cc	Urinary Sugar, Percent-age
Fasting	400	6.5	211	0
½ hr. after administration of 100 Gm of dextrose	500	5.5	274	Trace
1½ hr. after administration of 100 Gm of dextrose	526	7.0	364	4
3 hr. after administration of 100 Gm of dextrose	667	7.5	250	6.5

It will be noted that, while there was definite improvement in the condition of the patient and in the glycosuria, a definitely diabetic sugar curve persisted during estrogen therapy, although at a lower level.

<sup>14</sup> The estrogens used were estradiol benzoate (dihydroxyestrin benzoate), furnished by the Schering Corporation, and estrone (ketohydroxyestrin), furnished by Endo Products, Inc., through Dr. A. B. Tamis, of our endocrine and gynecologic clinic. The doses of estradiol benzoate are expressed in rat units of estrogen and those of estrone in international units. Five or more international units was found to be the equivalent of 1 rat unit. The average dose of estrone contained 10,000 international units and that of estradiol benzoate 2,000 rat units. These were given three times weekly.



The general condition of this patient, including the weight and the subjective symptoms, seemed to parallel the improvement in the diabetic state

CASE 2—Mrs J M, aged 51, was discovered to have diabetes during a routine urinalysis July 6, 1937 Urinary sugar at that time amounted to 26 per cent, and the fasting blood sugar was 352 mg per hundred cubic centimeters Menopausal symptoms began at about the same time The dextrose tolerance curve was as follows

	Blood Sugar, Mg /100 Cc	Urinary Sugar Percentage
Fasting	352	2
½ hr	500	25
1½ hr	512	3
3 hr	766	38

The patient was given a diet of carbohydrate 125 Gm, protein 74 Gm and fat 77 Gm, with 15 units of protamine zinc insulin daily This dose was later increased to 20 units, and the diabetes was satisfactorily controlled for several months On Jan 1, 1938 the glycosuria reappeared, the urinary sugar ranging from 1 to 2 per cent, with a fasting blood sugar of 286 mg per hundred cubic centimeters Because of marked flushes and other vasomotor symptoms she was given estrogen (10,000 international units) three times a week The diet and the doses of insulin remained the same This regimen was continued from February 1 to March 8 During this time the urine was sugar free Several weeks after withdrawal of estrogen, glycosuria reappeared, with the urinary sugar ranging from 15 to 3 per cent, despite use of a diet containing less carbohydrate—carbohydrate 100 Gm, protein 71 Gm and fat 70 Gm—and an increase of insulin to 30 units daily In August 1939 the dose was increased to 40 units daily, and the patient's urine became sugar free This state lasted only a short time, and on Sept 10, 1940, because of a return of glycosuria and aggravation of the menopausal symptoms, estrogen therapy was resumed, the diet and the insulin being kept at the same levels The urinary sugar was soon reduced to 0.2 per cent and less, remaining at these levels despite the fact that the dose of insulin had to be reduced finally to 20 units daily because of hypoglycemic reactions At about this time, too, an infection of the left foot developed, which healed promptly and was not accompanied by an aggravation of the diabetes On Sept 30, 1941 diethylstilbestrol, 1 mg twice daily, was substituted for estrone, with about the same results, but its administration had to be discontinued in December because of profuse vaginal bleeding

This patient showed a definitely beneficial effect on her diabetes from estrogen, with a lag in reestablishment of the condition after estrogen therapy was discontinued A later administration of estrogen was again effective in improving the diabetic state

CASE 3—Mrs S W, aged 50, was discovered to have glycosuria Nov 3, 1928 Urinary sugar at this time amounted to 35 per cent and blood sugar to 260 mg per hundred cubic centimeters Several months later the patient began to have flushes, menorrhagia, weakness, severe headaches and hypertension (blood pressure, 200 systolic and 100 diastolic) She was given a diet of carbohydrate 100 Gm, protein 71 Gm and fat 70 Gm, and despite the administration of 45 and later 50 units of regular insulin daily there was no appreciable change in the diabetic state Oral estrogen therapy was started June 11, 1939 This was also ineffective Several weeks later parenteral estrogen therapy (injection of 20,000 international units three times weekly) was substituted This was followed by such a marked reduction in the glycosuria that the dose of insulin had to be reduced to 10 units daily During this regimen the urinary sugar was reduced, the content ranging occasionally up to 0.5 per cent

Dextrose tolerance tests were done, the first before estrogen therapy and the latter after, with the following results

	Nov 14, 1938		Feb 13, 1941	
	Blood Sugar, Mg /100 Cc	Urinary Sugar, Percent- age	Blood Sugar, Mg /100 Cc	Urinary Sugar, Percent- age
Fasting	253	15	238	0.9
½ hr	400	30	333	25
1½ hr	500	35	345	0
3 hr	334	40	206	0



The administration of estrogen was discontinued May 20, 1941 and the dose of insulin increased to 40 and later 50 units because of continued glycosuria. The glycosuria increased during the profuse menstrual periods. In general the diabetic condition paralleled the menopausal symptoms.

This patient's diabetes was difficult to control without parenteral administration of estrogen. Oral administration of diethylstilbestrol was ineffective.

CASE 4—Mrs. A. A., aged 51, had had amenorrhea since January 1937. She was first seen by one of us (S. G.) on Feb. 25, 1938 because of diabetic symptoms, a urinary sugar content of 5 per cent and a blood sugar content of 550 mg per hundred cubic centimeters. For the previous two months she had suffered with severe vasomotor menopausal symptoms, mainly flushes and attacks of faintness. She had attended the Mount Sinai Hospital diagnostic service four years previously, where examination had given essentially negative results except to show a slight tremor. The basal metabolic rate was then normal. A diet containing carbohydrate 99 Gm, protein 79 Gm and fat 142 Gm was prescribed, and the patient's husband, a physician, was asked to give her 2,000 rat units of estrogen parenterally twice weekly. On March 7 her urine was sugar free, and so her diet was increased to carbohydrate 125 Gm, protein 89 Gm and fat 150 Gm, the use of estrogen being continued. The urine remained sugar free. The fasting blood sugar was 164 mg per hundred cubic centimeters on March 14 and 154 mg on March 28. On April 27 the urine was still sugar free, and the blood sugar was 113 mg per hundred cubic centimeters. On April 29 the patient began to menstruate for the first time since January 1937. She did not menstruate after that, although estrogen was still given. On November 4 her urine was sugar free and she was taking practically a normal diet, even eating cake at times and drinking some beer. On April 18, 1939 her blood sugar was 148 mg per hundred cubic centimeters. She has continued with estrogen, and her urine is sugar free unless estrogen is omitted, when glycosuria and menopausal symptoms reappear. She continues to take a practically unrestricted diet. In January 1942 oral administration of diethylstilbestrol was tried as a substitute for parenteral administration of estrogen, but this was ineffective in controlling glycosuria. A return to parenteral use of estrogen was again effective in controlling the diabetes.

This patient was never given insulin. From the start estrogen and diet were prescribed, and finally estrogen was given with a practically unrestricted diet and without insulin. Control of the diabetes, of the menopausal symptoms and of the general condition has been entirely satisfactory from Feb. 25, 1938 to the time of writing.

CASE 5—Mrs. I. R., aged 55, was discovered to have diabetes in 1935, the condition was so severe that with a diet of carbohydrate 100 Gm, protein 71 Gm and fat 70 Gm she required 60 units of regular insulin daily for control. This was satisfactory for about one year, when glycosuria appeared, with 3 to 5 per cent sugar in the urine, together with traces of acetone, and a fasting blood sugar content of 460 mg per hundred cubic centimeters. The amount of insulin had to be increased to 120 units daily, divided into four doses. On Sept. 3, 1940 the administration of estrogen was started in doses of 10,000 international units, later changed to 2,000 rat units, three times a week. Soon after this the dose of insulin was gradually reduced to 50 units of protamine zinc insulin and later to 35 units a day. With this regimen, the urinary sugar was maintained at about 1 per cent, with an occasional rise to 2 per cent. Dextrose tolerance tests gave the following results:

	Oct 15, 1940		July 29, 1941	
	Blood Sugar, Mg/100 Cc	Urinary Sugar, Percentage	Blood Sugar, Mg/100 Cc	Urinary Sugar, Percentage
Fasting	385	6	286	17
½ hr	500	7	420	25
1 hr	587	7.5	410	5
2 hr	665	7.5	364	5

After the onset of the menopause this patient had rather severe diabetes which was favorably influenced by estrogen therapy, although not as completely as in some of the other cases.

CASE 6—Mrs R S, aged 52, came to our diabetic clinic in March 1935. Her diabetes had been discovered several months before in another hospital, where she received a dose of 20 units of insulin daily in addition to a diet of 1,600 calories. Her complaints were loss of weight of about 10 pounds (4.5 Kg) in one year, irregularity of the menstrual periods of six months' duration and nervousness, melancholia and flushes of increasing frequency. Determination of the urinary sugar and the fasting blood sugar on March 5, 1935 revealed 4.3 per cent and 192 mg per hundred cubic centimeters, respectively. She was given a diet of carbohydrate 100 Gm, protein 70 Gm and fat 70 Gm and doses of insulin gradually increasing from 20 units to a maximum of 30 units, in two doses, daily. The patient was at all times uncooperative and often confessed to nonadherence to the diet and to omission of insulin. In spite of this she gained several pounds and the urinary sugar content came down to about 1 to 1.5 per cent. Because of the menopausal syndrome she was in the care of our endocrine department, where she was at first treated with sedatives, but in March 1937 her vasomotor disturbances became more pronounced and the urinary sugar rose until it reached a level of 3 per cent in a twenty-four hour specimen. Administration of estrogen, 10,000 international units, increased within a few weeks to 20,000 international units, three times weekly, was instituted on June 5. Insulin was withdrawn at the same time but had to be replaced in the regimen because of the glycosuria. She received estrogen for two years, until October 1939, during which she seldom needed more than 15 units to control her diabetes. The fasting blood sugar level on July 1, 1937

*Results of Dextrose Tolerance Tests*

Date	Results of Tests for Sugar	Fasting	Time After Dextrose			
			½ Hr	1½ Hr	2 Hr	3 Hr
September 1937	Blood (per 100 cc)	185 mg	266 mg	328 mg		287 mg.
	Urine	Trace	0.8%	7.5%		8.0%
Nov 6, 1937	Blood (per 100 cc)	182 mg	235 mg	312 mg	333 mg	
	Urine	Trace	Trace	2.0%	2.5%	
Jan 13, 1938	Blood (per 100 cc)	222 mg	286 mg	303 mg		308 mg.
	Urine	0	1.0%	2.5%		3.0%
Feb 1, 1938	Blood (per 100 cc)	175 mg	235 mg	333 mg		304 mg.
	Urine	0	Trace	3.0%		3.2%
April 13, 1939	Blood (per 100 cc)	174 mg	260 mg	274 mg		256 mg.
	Urine	0	0	2.5%		2.5%
April 10, 1940	Blood (per 100 cc)	110 mg	191 mg	156 mg		133 mg
	Urine	0	Trace	Faint trace		0
Feb 6, 1941	Blood (per 100 cc)	111 mg	191 mg	167 mg		98 mg
	Urine	0	0	0		0

was 191 mg per hundred cubic centimeters. On Oct 21, 1939 parenteral administration of estrogen was replaced by diethylstilbestrol therapy, 1 mg being given daily. The latter apparently controlled the vasomotor disturbances of the menopause but not the diabetes, because there was soon a return of glycosuria, with 1.5 to 2 per cent of urinary sugar. On Nov 14, 1940 administration of estrogen in doses of 10,000 international units was resumed, and it was continued for several months, during estrogen therapy the urinary sugar never rose above 0.5 per cent. The patient refused to submit to a dextrose tolerance test.

CASE 7—Mrs L F, aged 47, was discovered to have sugar in the urine in 1939 in a routine urinalysis. At that time she complained of the sudden onset of irregularity and profuseness of the menstrual flow, flushes and nervousness. The blood sugar was 300 mg per hundred cubic centimeters and the urinary sugar 2.8 per cent. At first a low caloric diet relatively high in carbohydrates and amounting to about 1,600 calories per day controlled the diabetes and reduced the urinary sugar to about 1 per cent. From the onset the patient refused to take insulin. In December 1940 the glycosuria increased, and at that time the blood sugar content was 333 mg per hundred cubic centimeters. Diethylstilbestrol, 5 mg daily, in addition to the aforementioned diet was tried, with no apparent improvement in the glycosuria, the urinary sugar ranging from 2 to 3 per cent. Estrogen, 2,000 rat units three times a week, was substituted, and within two weeks the urine became sugar free, and it remained so except for occasional rises to about 0.5 per cent.

This patient had a good response to estrogen given parenterally but not orally.

CASE 8—Mrs S R, aged 50, came to the outpatient department in 1937 because of irregularity of menstrual periods, weakness, nervousness, irritability and a progressive gain in weight. At that time there was 2.5 per cent sugar in the urine and the fasting blood sugar was 185 mg per hundred cubic centimeters. She was given a diet of carbohydrate 125 Gm, protein 71 Gm and fat 70 Gm, and from September 7 was given 10,000 international units of estrogen three times a week. She refused to take insulin. Estrogen therapy was continued until February 1939. During this period the urine was sugar free with few exceptions and the sugar tolerance curve gradually returned to an approximate normal. The results of dextrose tolerance tests are shown in the table.

This patient responded rather well to estrogen therapy and diet without the use of insulin. The dextrose tolerance curves paralleled the improvement in the glycosuria. This did not always happen in patients who showed improvement.

## 2 DIABETES AGGRAVATED BY THE MENOPAUSE

CASE 9—Mrs A L, aged 47, was discovered to have diabetes in 1937, and from then until 1940 she received 10 units of insulin daily and a diet of carbohydrate 100 Gm, protein 71 Gm and fat 70 Gm. This treatment controlled her diabetic condition. The urinary sugar was reduced from 3 to 0.5 per cent or none, and the results of repeated tests of the fasting blood sugar ranged between 250 and 161 mg per hundred cubic centimeters. The level March 15, 1937 was 170 mg. The patient continued on this regimen until 1940, when she began to have flushes, became irritable, experienced attacks of palpitation and noticed a periodic irregularity and relative scantiness in the menstrual flow. Concomitantly the urinary sugar rose to 2.5 per cent and the fasting blood sugar to 199 mg per hundred cubic centimeters, and a month later the latter was 250 mg. Because of the patient's refusal to take additional injections she was given 5 mg of diethylstilbestrol orally daily. Within one week the glycosuria disappeared and the fasting level of blood sugar dropped to 130 mg per hundred cubic centimeters. There were no unpleasant reactions to diethylstilbestrol, but because of the patient's failure to cooperate no dextrose tolerance tests were performed. She discontinued treatment against our advice in November 1940, because of nausea, but when her climacteric symptoms and glycosuria reappeared a short time later she resumed it until July 1941 with good results. At the time of writing she still refuses parenteral estrogen therapy.

This patient is the only one in the group who seemed to benefit from diethylstilbestrol, given orally.

CASE 10—Mrs M W, aged 59, was discovered to have diabetes nine years ago. Then the urinary sugar was 2 per cent and the blood sugar 217 mg per hundred cubic centimeters. A diet of carbohydrate 100 Gm, protein 71 Gm and fat 70 Gm was sufficient to render the urine sugar free and reduce the blood sugar to 154 mg per hundred cubic centimeters.

In 1938, about the time of the onset of the menopause, the sugar content of the urine rose to 3 per cent. Estrogen therapy was begun on October 18 and discontinued May 28, 1941 (10,000 international units three times a week). During the entire period of estrogen therapy the urine was sugar free and the blood sugar never rose above 80 mg per hundred cubic centimeters. The patient refused to take insulin. After cessation of the estrogen therapy glycosuria reappeared (1 to 3 per cent of urinary sugar) and the fasting blood sugar ranged between 160 and 180 mg per hundred cubic centimeters.

This patient whose diabetes was aggravated by the menopause refused insulin but responded well to treatment with estrogen and diet alone.

## 3 DIABETES APPEARING LONG AFTER THE MENOPAUSE

CASE 11—Mrs L K, aged 53, whose menopause began in 1926, was discovered to have diabetes at the clinic of Mount Sinai Hospital in 1929. Up to March 4, 1940 a diet of carbohydrate 100 Gm, protein 65 Gm and fat 60 Gm controlled her diabetes, but after that glycosuria developed in spite of the diet. In September 1940 her blood sugar amounted to 286 mg per hundred cubic centimeters and her urinary sugar to 1 per cent. Diethylstilbestrol was given for several weeks, with no apparent improvement in the glycosuria. The substitution of insulin, at first 10 and then 15 units daily, is controlling her diabetic state at the time of writing. The blood sugar on Feb 2, 1941 was 140 mg per hundred cubic centimeters, and since then her condition has not changed appreciably. No estrogen was used parenterally.

The diabetes of this patient was discovered three years after the menopause, and that was thirteen years before her appearance at our clinic. Diethylstilbestrol failed to influence her diabetes.

CASE 12—A LoB, aged 59, came to our clinic on Sept 12, 1939, after the discovery of 4 per cent sugar in the urine and a fasting blood sugar content of 222 mg per hundred cubic centimeters. At first a diet of carbohydrate 100 Gm, protein 71 Gm and fat 75 Gm and 25 units of protamine zinc insulin controlled the diabetes, and she gained several pounds. Within two months after the institution of this regimen the glycosuria returned and could be controlled only by 40 units of protamine zinc insulin or more daily. Estrogen, 10,000 international units given three times weekly, was tried, in addition to the original 25 units of insulin, and was administered from August 27 until December 1940, when, because of no change in the diabetic condition, estrogen was withdrawn and the insulin increased to 35 units daily. At present the patient receives 40 units of protamine zinc insulin once daily, with fairly good results, the urinary sugar never reaching 1 per cent.

CASE 13—Mrs R S, aged 65, had had diabetes of ten years' duration. She had passed through the menopause twenty-five years before. In spite of her obesity and myxedematous appearance, the basal metabolic rate on three different occasions was +31, +40 and +22 per cent, respectively. She had a marked polyuria, excreting 128 ounces (3,800 cc) or more of urine daily. The urine continued to have a low specific gravity. The polyuria could be controlled only with pitressin. The diabetes was controlled with 20 to 30 units of insulin daily and a diet of carbohydrate 125 Gm, protein 70 Gm and fat 70 Gm. A dextrose tolerance test on Jan 8, 1935 gave the following results:

Fasting	Blood Sugar, Mg /100 Cc	Urinary Sugar, Percentage
	154	0
½ Hr	323	0
1 Hr	362	0
2½ Hrs	328	0

The fasting blood sugar level on March 24, 1937 and on May 4, 1938 was 240 mg and 200 mg per hundred cubic centimeters, respectively, in spite of the persistent absence of sugar in the urine. At that time roentgen examination of the head was undertaken, and the report reads, "Destruction of posterior clinoid processes due very likely to tumor" (Dr S F Weitzner). In 1940 sugar began to appear in the urine and persisted, in spite of an increase in the dose of insulin to 50 units daily. On February 20 estrogen therapy was added, 10,000 international units being given three times weekly. During this therapy the patient's urine remained sugar free, but, because of the return of polyuria, pitressin had frequently to be substituted for the estrogen, as the patient refused to take both. With the return to administration of the former the polyuria subsided but the glycosuria recurred. The patient was particularly anxious to receive pitressin and begged for it at each clinical session. This was because she dribbled urine even on the street when the polyuria was severe.

The diabetes of this patient appeared years after the menopause but might have been related to the evident pituitary disease and therefore responsive to estrogen.

#### 4 DIABETES UNRELATED TO THE MENOPAUSE AND ALLERGY (?) TO INSULIN

CASE 14—Mrs B S, aged 52, had had diabetes for many years. Until four years earlier this had been controlled by a diet of carbohydrate 105 Gm, protein 60 Gm and fat 60 Gm. Then 25 units of insulin daily had to be added, although the patient continued to adhere to her diet. However, soon after the institution of insulin therapy its use was discontinued because of the generalized pruritus that followed each injection and the severe local reactions at the site of the injection. The allergy clinic found marked sensitivity to pork. Crystalline insulin produced the same reaction. Estrogen was tried because of the difficulty in controlling the diabetes by diet alone. This was given for eight months. The glycosuria was never appreciably reduced.

CASE 15—Mrs D W, aged 47, was discovered to have diabetes five years before and had so far been without vasomotor menopausal disturbances. Her reactions to insulin were similar to those in case 14, and estrogen was tried and again found disappointing.

Neither of these patients had menopausal symptoms, they were chosen for treatment because insulin could not be used. Estrogen was tried but had no effect on the diabetes.

## COMMENT

As the literature on the treatment of diabetes with estrogenic hormone has been so contradictory, it was felt that an effort should be made to select the proper patient for such treatment. It was for this reason that our patients were divided into the following four groups: (1) those in whom the onset of diabetes coincided with that of the menopause, (2) those in whom existing diabetes was aggravated by the menopause, (3) those in whom the diabetes appeared long after the menopause and (4) 2 who had had no menopausal symptoms but who could not take insulin because of severe local reactions, presumably allergic.

Thus, of our 15 patients 8 had a concomitant onset of diabetes and the menopause, 2 had diabetes aggravated by the menopause and in 3 diabetes appeared long after the menopause. The 2 patients whose existing diabetes was aggravated by the onset of the menopause were of particular interest because they demonstrated the effect of estrogen on diabetes aggravated by this phase of pituitary activity in contradistinction to that which has developed some years after the menopause and therefore presumably in the quiescent phase of the anterior lobe of pituitary gland. Patient 13 is of separate interest because she was intensively studied for several years from the standpoint of concomitant diabetes mellitus and diabetes insipidus. She had extreme polyuria which did not parallel the grade of her glycosuria and which, indeed, antedated her diabetes. When her urine was sugar free and she was still having polyuria, the specific gravity of her urine was much below 1.010, usually 1.002 to 1.004. Control of the polyuria was obtained readily with pitressin, although this would be expected to increase glycosuria and with it polyuria.

The patients with concomitant diabetes and the menopause all responded favorably to estrogen, as well as those with aggravation of diabetes at the time of the menopause. Patient 13, whose diabetes came on long after the menopause, was also benefited, because she had definite pituitary disease. The other 2 patients with onset of diabetes long after the menopause were not thus benefited. The two allergic patients, too, showed no response to estrogen therapy.

The diagnosis of the menopause was assumed on the basis of subjective complaints, such as headaches, flushes, palpitation, emotional instability, perspiration, vague muscle pain and disturbances of the menstrual rhythm.

Throughout the period of study a pragmatic course was followed and the results were gaged from analysis of the urine and blood and observation of the general condition and weight of the patient. No patient was exposed to lack of control of her diabetes by use of insufficient insulin. The elimination of insulin was accomplished gradually.

Our findings agree with those of Mazer and Israel that the glycosuria and hyperglycemia can be controlled only by large doses of estrogen. Only 1 patient received 30,000 international units of estrogen weekly. The others required from 60,000 to 80,000. The response to estrogen was the same with estrone (keto-hydroxyestrin) and estradiol benzoate (dihydroxyestrin benzoate) provided large doses were given.

Improvement in the diabetes closely paralleled that of the menopausal symptoms. Subjective improvement was always accompanied by marked reduction of glycosuria and hyperglycemia. The urine frequently became sugar free.

Our experience with diethylstilbestrol given by mouth was limited because of the recent introduction of this substance for clinical trial, but if one judges from the scanty available data its effect on hyperglycemia does not parallel its effect on menopausal symptoms. It would be interesting to compare the effect of oral

and of parenteral administration Mazer, Israel and Ravetz<sup>15</sup> have recently reported their observations on the parenteral use of diethylstilbestrol They found its effect the same as that of estrogen

There remains the broad question as to what patients may be treated with estrogen Can we say that the patient who has severe climacteric symptoms and diabetes is the one, or shall we conclude that the suitable patient is the one whose diabetes comes on at about the same time as the menopause? This work with a limited number of subjects rather indicates that the proper patients for this treatment are those in whom diabetes develops at about the same time as the menopause or those with aggravation of diabetes at this period Careful work at various clinics will clarify this question

In conclusion it must be stated that treatment of diabetes with estrogen must not be lightly undertaken It must be carried out only by physicians with a thorough knowledge of the problems involved, and with careful observation of the patient It should not be generally undertaken until all the problems concerned with its use have been solved

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<sup>15</sup> Mazer, C , Israel, S L , and Ravetz, E    The Synthetic Estrogen Stilbestrol, J A M A **116** 675-681 (Feb 22) 1941

# Progress in Internal Medicine

## BLOOD

### A REVIEW OF THE RECENT LITERATURE

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(Concluded from Page 145)

### SPLENIC DISORDERS

*Banti's Syndrome*—An instance of Banti's disease due to stenosis of the portal vein without hepatic cirrhosis is reported by Trimble and Hill<sup>318</sup>. The postmortem observation of mechanical congestive splenomegaly lends further support to the view of Thompson that hypertension of the portal vein is the common denominator of so-called Banti's disease. The portal hypertension results in splenomegaly, collateral circulation and the development of esophageal varices. Churchill<sup>319</sup> cites a 24 year old man who had ascites, anemia, leukopenia, thrombopenia and splenomegaly. Splenectomy was performed, and the patient died with bronchopneumonia during the postoperative period. The spleen was shown to contain increased amounts of fibrous tissue and the splenic vein hyalinized plaques of intimal thickening. Pemberton<sup>320</sup> reports the outcome in 226 cases in which splenectomy was performed at the Mayo Clinic for splenic anemia and Banti's disease. The mortality rate for the operation was 12.4 per cent. The survival period was as follows: five years in 55.1 per cent of the cases, ten years in 43.2 per cent, twenty years in 22.7 per cent. Fully 50 per cent of the patients who experienced gastrointestinal hemorrhages before operation had recurrence of hemorrhages after operation. The deaths of one third of the patients were directly attributable to hemorrhages.

An increased number of target cells in the blood of dogs and guinea pigs was observed by Miller, Singer and Dameshek<sup>321</sup> after removal of the spleen and after either incomplete or complete ligation of the splenic vein. The greatest number of target cells were seen in dogs after splenectomy and the fewest after incomplete ligation of the splenic vein. No target cells were noted, although Howell-Jolly bodies were present, in rabbits' blood after splenectomy. The relationship of the spleen to the morphologic picture of blood regeneration was the subject of

318 Trimble, W K, and Hill, J H. Congestive Splenomegaly (Banti's Disease) Due to Portal Stenosis Without Hepatic Cirrhosis, Aneurysms of the Splenic Artery. Report of a Case with Necropsy, Arch Path **34** 423 (Aug) 1942

319 Churchill, T P. Banti's Syndrome, Texas State J Med **37** 720, 1942

320 Pemberton, J deJ. The Present Status of Surgery of the Spleen, Cincinnati J Med **22** 564, 1942

321 Miller, E B, Singer, K, and Dameshek, W. Experimental Production of Target Cells by Splenectomy and Interference with Splenic Circulation, Proc Soc Exper Biol & Med **49** 42, 1942

a study by Cruz and Robscheit-Robbins<sup>322</sup> The spleens were removed from dogs, which later were made anemic either by the administration of acetylphenylhydrazine or by hemorrhage The normoblastic response of the splenectomized animals during the initial phase of the regeneration of the blood was four times as great as that observed in normal dogs, and primitive erythroblasts were found in much greater numbers The authors suggest a relation between the function of the spleen and either the maturation of erythroblasts in the marrow or the release of new red blood cells into the circulation

*Gaucher's Disease*—An instance of Gaucher's disease with hemolytic anemia and thrombopenia is reported by Mandelbaum, Berger and Lederer<sup>138</sup> The spleen, weighing 6,822 Gm, was removed at operation, and subsequently the blood values rose to normal No Gaucher cells were found in the bone marrow Lipid analysis of this spleen was undertaken by Sobel and Kaye<sup>323</sup> The characteristic lipid constituent, kersin, was isolated and identified, and an increase of the cerebroside at the expense of neutral fat was found Danielson, Hall and Everett<sup>324</sup> report the isolation of a kersin-like cerebroside containing d-dextrose rather than d-galactose from the spleen of a 4 year old girl with Gaucher's disease The authors point out that their finding and others recently reported suggest that the synthesis of a glucoside type of splenic kersin is a frequent occurrence in this disease

Emanuel<sup>325</sup> stresses the diagnostic value of aspirated sternal marrow in suspected cases of Gaucher's disease The characteristic large Gaucher cells were found by the author in the marrow of 2 men aged 30 and 35 years, respectively The platelet count was depressed and the coagulation time was prolonged in both cases Transient leukocytosis, the white blood cell count attaining 50,000 per cubic millimeter, was noted in 1 case Gaucher cells were found on biopsy of a suspected lesion of bone by Reed and Sosman<sup>326</sup> Myer<sup>327</sup> reports the postmortem observations in a 7 year old child with Gaucher's disease The mediastinal and hilar glands were enlarged and contained masses of the pathognomonic cells During life a severe productive cough had been noted, and necropsy revealed extensive invasion of the lungs by the disease process Reisman and Utz<sup>328</sup> were unable to find Gaucher cells in the sternal marrow of a 10 year old girl with the disease, but the typical cells were seen in splenic tissue obtained by puncture of the spleen Rapid increase in the size of this organ eventually led to splenectomy, but the bone lesions, characteristic of the disease, continued to progress

#### HEMORRHAGIC DISORDERS AND BLOOD COAGULATION

*General Observations*—Classifications of the hemorrhagic diseases are presented by Lozner,<sup>329</sup> Jurgens<sup>330</sup> and Dam<sup>331</sup> The diagnosis, the clinical manifes-

322 Cruz, W O, and Robscheit-Robbins, F S Relationship Between the Spleen and the Morphologic Picture of Blood Regeneration, *Am J M Sc* **203** 28, 1942

323 Sobel, A E, and Kaye, I A Gaucher's Disease A Case with Hemolytic Anemia and Marked Thrombopenia, Improvement After Removal of Spleen Weighing 6,822 Grams, Lipid Analysis of the Gaucher's Spleen, *Ann Int Med* **16** 446, 1942

324 Danielson, I S, Hall, C H, and Everett, M R Glucoside Type of Cerebroside in the Spleen in Gaucher's Disease, *Proc Soc Exper Biol & Med* **49** 569, 1942

325 Emanuel, E Gaucher's Disease Report of Two Unrelated Cases, *Edinburgh M J* **48** 843, 1941

326 Reed, J, and Sosman, M C Gaucher's Disease, *Radiology* **38** 579, 1942

327 Myer, B Gaucher's Disease of the Lungs, *Brit J Child Dis* **38** 135, 1941

328 Reisman, H A, and Utz, D W Gaucher's Disease Report of Case, *Arch Pediat* **59** 446, 1942

329 Lozner, E L Hemorrhage and Hemorrhagic Diathesis, *U S Nav M Bull* **40** 641, 1942



tations and the treatment of these conditions are covered by Pepin and collaborators<sup>332</sup> and by Lessard<sup>333</sup>. Kugelmass<sup>334</sup> outlines the clinical characteristics and discusses the treatment of the hemorrhagic diseases as encountered in children.

The role of vitamins in the hemorrhagic states is discussed by Scarborough<sup>335</sup>. Vitamin D has been shown to reduce the bleeding time in jaundiced patients when the Ivy method is employed. This vitamin is also thought to influence the formation of clot. Vitamin C rapidly controls the hemorrhagic manifestation in scurvy, but earlier reports that it exerted a beneficial effect in thrombopenic purpura have received little recent confirmation. Dam<sup>331</sup> reports that chicks on a diet deficient in vitamin E had accumulations of plasma under the skin. Except for alphatocopherol, all known vitamins, including eriodictin and hesperidin, in which vitamin P is thought to reside, proved ineffective in protecting against the disease.

*Essential Thrombopenic Purpura*—The occurrence of an acute form of thrombopenic purpura which differed from the usual essential type of the disease by rapid progression, presence of icterus, cerebral manifestations and failure to respond to transfusions or splenectomy is reported by Altschule<sup>336</sup> in a 50 year old woman with terminal manifestations of intracranial disease, icterus, rapidly progressive anemia, purpura and fever. Transfusions and splenectomy did not arrest the process, and necropsy revealed a large number of thrombotic lesions made up of masses of platelets within the capillaries and to a lesser extent within the arterioles. The cause of the change in the vascular endothelium resulting in the deposition of platelets is not known. It is suggested that the profound thrombopenia seen in this type of purpura may be due to withdrawal of enormous numbers of platelets from the circulation. That a similar phenomenon occurs in other forms of thrombopenia, but in a less easily detected form, is suggested by the author.

Whitney and Barritt,<sup>337</sup> reviewing the literature, found 14 reported cases of congenital thrombopenic purpura, to which they add 2 new cases. The first child, born to a mother who had undergone splenectomy for thrombopenic purpura twelve years prior to her pregnancy, was covered with purpuric spots at birth and died on the third day of life. A platelet count of 80,000 per cubic millimeter, a bleeding time of one and one-half minutes and a coagulation time of three and one-half minutes were recorded. A second pregnancy ensued, and this infant likewise showed petechiae at birth. The platelet count was 90,000 per cubic millimeter, and the bleeding time was eleven minutes and the coagulation time one and one-half minutes, and the prothrombin value was 28 per cent of normal.

330 Jurgens, R. Systematik der hamorrhagischen Diathesen, Schweiz med Wchnschr **71** 1494, 1941.

331 Dam, H. Factors in Preventing the Blood from Leaving the Vascular System, Quart Bull Indiana Univ M Center **3** 43, 1942.

332 Pepin, J. R., Lefebvre, R., Dandurand, R., and Dussault, R. Les grands syndromes hamorrhagiques, Union med du Canada **71** 251, 1942.

333 Lessard, R. Symposium on the Hemorrhagic Syndromes. The Hemorrhage from Blood Dyscrasia, Union med du Canada **71** 1267, 1942.

334 Kugelmass, I. N. Hemorrhagic Problems in Child Surgery, Am J Clin Path **12** 467, 1942.

335 Scarborough, H., in Discussion on Vitamins and Hæmorrhagic States, Proc Roy Soc Med **35** 407, 1942.

336 Altschule, M. D. A Rare Type of Acute Thrombocytopenic Purpura. Widespread Formation of Platelet Thrombi in Capillaries, New England J Med **227** 477, 1942.

337 Whitney, L. H., and Barritt, A. S. Spontaneous and Hereditary Thrombopenic Purpura in a Mother and Two Sons, Am J Dis Child **64** 705 (Oct) 1942.

Despite blood transfusion and the administration of vitamin K, this child succumbed twenty-four hours after birth. Postmortem examinations were made on both infants.

Urbanski and Hutner<sup>338</sup> observed a mother with chronic thrombopenic purpura whose first pregnancy terminated in the birth of a stillborn child. The infant was covered with petechial hemorrhages, and at necropsy there were seen extensive subarachnoid, subpleural and subpericardial hemorrhages. On the nineteenth postpartum day, profuse vaginal bleeding commenced, which necessitated splenectomy. The mother made an uneventful clinical recovery, although no platelet counts of over 100,000 per cubic millimeter were recorded during a two year follow-up period. A second pregnancy ensued two and a half years after the removal of the spleen. The infant showed petechiae on the face and on the buccal membranes at birth and had a bleeding time of five and one-half minutes and a platelet count of 23,000 per cubic millimeter. The petechiae rapidly disappeared, and the infant developed normally. The mother had a normal postpartum course and subsequently underwent two further pregnancies, with normal infants in each instance.

The spleen was removed in 11 cases of chronic idiopathic purpura by Phillips and Zions<sup>339</sup>. One patient died, another was alive eight months postoperatively, but the hemorrhagic tendency was unaltered, the remaining 9 patients showed complete cure. Acute thrombopenia was observed in 5 patients, with recovery following transfusions in 4 and a fatal termination in the fifth. Splenectomy was not done if the disease was in an acute form. The importance of making careful diagnostic studies before splenectomy, to rule out symptomatic purpura, is stressed.

Evans<sup>340</sup> reports successful arrest of acute hemorrhagic thrombopenic purpura following splenectomy. Taylor<sup>341</sup> calls attention to instances of purpura haemorrhagica in which severe and protracted menorrhagia is the only clinical manifestation of the disease.

Ligation of the splenic artery for thrombopenic purpura is discussed by Berg and Rosenthal,<sup>342</sup> who tried the procedure in 2 cases, without any hematologic and only transient clinical improvement resulting. Splenectomy was necessitated in both instances because of the return of symptoms. One case terminated fatally.

Wiseman and Doan<sup>343</sup> call attention to the syndrome which they named primary splenic neutropenia. The underlying etiologic factor is said to be a hypersplenic state wherein the function of the spleen in destroying abnormal or senile cells is augmented by pathologic destruction of normal elements. Such a mechanism is suggested as responsible for thrombopenic purpura as well as for congenital hemolytic icterus and splenic neutropenia, with, in each instance, selective pathologic phagocytosis of a specific cellular element.

338 Urbanski, A. X., and Hutner, C. I. Thrombopenic Purpura Complicating Pregnancy. Treatment by Splenectomy Resulting in Clinical Cure and Followed by Three Full Term Pregnancies, *J. A. M. A.* **120** 754 (Nov. 7) 1942.

339 Phillips, J. R., and Zions, M. A. Thrombocytopenic Purpura, *Am. J. Surg.* **57** 51, 1942.

340 Evans, R. L. Splenectomy in Thrombocytopenic Purpura, *Guthrie Clin. Bull.* **12** 56, 1942.

341 Taylor, W. W. Thrombocytopenic Purpura as a Cause of Uterine Bleeding, *Memphis M. J.* **17** 182, 1942.

342 Berg, A. A., and Rosenthal, N. Ligation of the Splenic Artery for Thrombocytopenic Purpura and Congestive Splenomegaly, *J. Mt. Sinai Hosp.* **8** 382, 1942.

343 Wiseman, B. K., and Doan, C. A. Primary Splenic Neutropenia. A Newly Recognized Syndrome, Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura, *Ann. Int. Med.* **16** 1097, 1942.

Studies of the action of extracts from the spleens of patients with thrombopenic purpura on the platelets and hemopoietic organs of rabbits are reported by Paul<sup>344</sup> Extracts of five spleens were prepared according to the method of Troland and Lee and were given to the rabbits by vein A transient fall in the platelet count was observed eight hours after the injection, followed by a return to the preinjection level within twenty-four hours Bone marrow sections and imprints revealed no significant change in the number of the megakaryocytes or in their structure

Uihlein<sup>345</sup> likewise failed to demonstrate clearly or to deny definitely the presence of a thrombocytolytic substance in acetone extracts of spleens removed from patients with idiopathic thrombopenic purpura Of 13 such splenic extracts administered intravenously to rats, 2 produced a considerable drop and 3 a moderate decrease in the number of circulating platelets Of extracts from the spleens of 5 patients with hemolytic icterus, only 1 produced a decrease in platelet count This response was consistent in all animals treated, and the active principle was not destroyed by heat In all, 28 extracts were prepared, including 4 from normal spleens, 1 from liver and 1 from some lymph tissue as control material Twenty-two extracts failed to produce significant thrombopenia, but all animals appeared apathetic for short periods after receiving an injection Because of the inconsistency of the results, the author feels that a new method of extraction of "thrombocytopen" is essential before any final conclusion can be made

*Secondary Thrombopenic Purpura*—A case of thrombopenic purpura secondary to carcinomatous replacement of the bone marrow is reported by Willis<sup>346</sup> The primary site of the neoplasm was the stomach Fifteen other instances of carcinoma of the stomach associated with secondary thrombopenic purpura were collected from the literature Often the carcinoma was not discovered until autopsy

Thrombopenic purpura following the administration of sulfathiazole is reported by two authors Rosenfeld and Feldman<sup>347</sup> observed profuse bleeding from the nose and the mouth, hematuria and extensive petechiae in a 37 year old man after 55 Gm of sulfathiazole had been administered during a three day period The platelet count declined to 2,000 per cubic millimeter, the bleeding time was six minutes Following withdrawal of the drug there were prompt recovery and return of the platelet count to normal, and two weeks later 15 Gm of sulfathiazole was given in a five day period without recurrence of purpura Werner<sup>348</sup> reports thrombopenic purpura following sulfathiazole in a 16 year old boy This patient received 139 Gm of sulfathiazole during a period of seven days, with the appearance of a slight rash on the fifth day An uneventful recovery from the infection of the upper respiratory tract followed Six weeks later 10 Gm of sulfathiazole was administered, and within twelve hours purpura and gingival bleeding developed The platelets disappeared from the blood, and a bleeding time of thirty-five minutes was recorded Conservative therapy, without specific measures, resulted in complete recovery

344 Paul, J T Effect of Splenic Extracts from Cases of Essential Thrombocytopenic Purpura on the Platelets and Hematopoietic Organs of Rabbits, *J Lab & Clin Med* **27** 754, 1942

345 Uihlein, A Effect of Injection of Tissue Extracts on the Number of Blood Platelets, *J Lab & Clin Med* **28** 157, 1942

346 Willis, W H Thrombocytopenic Purpura and Carcinoma of Stomach Report of a Case with Purpura Appearing After Subtotal Gastrectomy, *Ann Int Med* **16** 782, 1942

347 Rosenfeld, S, and Feldman, F Thrombocytopenic Purpura Due to Sulfathiazole, *J A M A* **118** 974 (March 21) 1942

348 Werner, W I Thrombocytopenic Purpura Following Administration of Sulfathiazole Case Report, *Southwestern Med* **26** 49, 1942

Sulfadiazine caused acute thrombopenic purpura in a patient seen by Whitehouse and Watkins<sup>349</sup>. A 37 year old man with a pulmonary abscess had received an earlier course of sulfathiazole. Sulfadiazine was instituted in three short courses, and after the second there developed thrombopenia and bleeding from the gums. After recovery, four and one-half weeks later, a third course of sulfadiazine was begun. The ingestion of 7 Gm in forty-eight hours caused the platelet count to drop from a normal level to 138,000 per cubic millimeter. The administration of the drug was discontinued, and no further hematologic phenomena developed.

Varas<sup>350</sup> reports the case of a 4 year old child with malaria in whom hemorrhagic purpura developed following the administration of 16.5 Gm of quinine. An instance of thrombopenic purpura complicating antisyphilitic arsphenamine therapy is reported by Laird<sup>351</sup>. Graeber<sup>352</sup> presents 3 cases of thrombopenic purpura following the ingestion of sedormid (allylisopropylacetylcarbamide). The literature is briefly reviewed, and 15 additional cases are tabulated. Thiel<sup>353</sup> observed a case following the administration of sedormid and another following the administration of saridon, an anesthetic containing sedormid. Infectious mononucleosis associated with acute thrombopenic purpura was seen by Magner and Brooks<sup>214</sup>. The sternal marrow was studied in 10 patients by Moeschlin<sup>354</sup> during experimental tolerance tests with sedormid. A slight change to younger forms developed in the megakaryocyte series immediately after the development of acute thrombopenia. Two or three days later a progressive increase in the blood platelets was noted in the peripheral blood, consisting of pathologic and large forms. In hypersensitive patients sedormid produced thrombopenia in from thirty to sixty minutes. The author failed to demonstrate a lysin for platelets as a feature of acute thrombopenia.

*Nonthrombopenic Purpura*—Barnes and Duncan<sup>355</sup> report a case of non-thrombopenic purpura with involvement of viscera, skin and joints. Laparotomy was done before the diagnosis was apparent. The ileum was seen to be greatly congested, with many subperitoneal hemorrhages, suggesting regional ileitis. The patient recovered. An instance of Henoch's purpura was reported by Quirno Lavalle and Mallo Huergo<sup>356</sup>. Looper<sup>357</sup> observed a 31 year old man who died with profuse pulmonary hemorrhages. Except for hematuria, no other evidence of a tendency toward bleeding was present. The platelet count was 712,800 per cubic millimeter. Necropsy showed evidence of purpura in the lungs, with no other abnormality present to account for the fatal bleeding.

349 Whitehouse, F. R., and Watkins, C. H. Acute Thrombocytopenic Purpura Following Sulfadiazine Therapy. Report of Case, Proc. Staff Meet., Mayo Clin. **17** 140, 1942.

350 Varas, R. P. Hemorrhagic Purpura from Quinine Poisoning, Bol. Soc. cubana de pediat. **14** 49, 1942.

351 Laird, S. M. Thrombocytopenic Purpura Complicating Arsenobenzene Therapy, Brit. M. J. **1** 381, 1942.

352 Graeber, W. Thrombopenische Blutungen nach Sedormidegebrauch, Munchen med. Wchnschr. **89** 122, 1943.

353 Thiel, W. Akute thrombopenische Purpura nach Sedormid- und Saridongebrauch, Munchen med. Wchnschr. **89** 934, 1942.

354 Moeschlin, S. Die Sedormid-Thrombozytopenie anhand von Sternalpunktaten, Belastungs- und Transfusionsversuchen, Schweiz. med. Wchnschr. **72** 119, 1942.

355 Barnes, C. G., and Duncan, G. W. Anaphylactoid Purpura Simulating Acute Regional Ileitis, Brit. J. Surg. **29** 253, 1941.

356 Quirno Lavalle, R., and Mallo Huergo, E. Síndrome abdominal agudo en el curso del purpura, Prensa med. argent. **29** 590, 1942.

357 Looper, E. A. Bronchial Involvement in Purpura Hemorrhagica, Ann. Otol., Rhin. & Laryng. **51** 1106, 1942.

The clinical characteristics of Werlhof's disease were present in a patient seen by Reimann<sup>358</sup>. An uncontrollable and fatal hemorrhagic diathesis ensued, despite the fact that the bleeding and clotting times, the number of platelets, the fibrinogen content of the plasma and the level of vitamin C in the blood were normal. A thrombolytic principle was demonstrated in the patient's plasma which when added to normal blood caused dissolution of the clot. It was suggested that this thrombolytic activity was responsible for the hemorrhagic diathesis.

Lucia and Aggeler<sup>359</sup> discuss the history of bruising following slight trauma in patients who do not have spontaneous purpura. "Single easy bruisability," as the authors designate the condition, occurs predominantly in women. The skin of the patients is usually fair, thin and unduly sensitive to light. No symptoms of a hemorrhagic disorder are present except for infrequent attacks of epistaxis and gingival bleeding after brushing the teeth, but excessive bleeding may occur following tonsillectomy or extraction of a tooth. Twenty-three patients were studied to detect any abnormalities indicative of a tendency toward bleeding, and the most significant finding was a slight prolongation of the bleeding time in six cases. The authors feel that simple, easy bruisability was due not to a defect in the blood but to thinness of the skin and defective cushioning of the subcutaneous vascular bed. The symptom may disappear spontaneously but is occasionally present from childhood as a lifelong affliction.

*Hemophilia*—Lyophilized plasma is as effective as citrated blood in reducing the coagulation time in hemophilia, according to Johnson<sup>360</sup>. The successful management of hemarthrosis, hematuria and hemorrhage following extraction of teeth with lyophilized plasma is reported. The administration of this prepared plasma likewise proved effective in prophylaxis against recurrent hemorrhage. The coagulation time is lowered rapidly, as with citrated blood, the maximum decrease occurs within fifteen minutes. To prevent loss of thromboplastic activity, the plasma should be frozen and dried within a few hours after its removal from the donor. The lyophilized material may be stored at 5 C for at least three months without deterioration. Transfusions of 125 to 150 cc of reconstituted plasma exerted maximum therapeutic benefit, and larger amounts did not produce any further decrease in coagulation time.

The clot resistance was found by Copley and Lalich<sup>361</sup> to be decreased in 2 patients with hemophilia. The clot resistance was determined by a method of the authors described elsewhere (page 205). No direct relation was observed between the coagulation time and the clot resistance. The subcutaneous injection of extracts of bursa pastorens (shepherd's purse) combined with transfusions of blood increased the clot resistance. The hemostatic action of bursa pastorens may depend on several principles, as it contains oxalic acid, dicarboxylic acid and phytothrombin.

Norcross<sup>362</sup> studied a patient with hemophilia associated with vitamin C deficiency. The decreased capillary resistance to negative pressure was corrected

358 Reimann, F. Purpura Thrombolytica. Ein Beitrag zur Pathogenese der hamorrhagischen Diathese, *Acta med Scandinav* **107** 95, 1941.

359 Lucia, S. P., and Aggeler, P. M. Simple Easy Bruisability. A Pseudo-hemorrhagic Diathesis of Probable Endocrine Origin, *J Clin Endocrinol* **2** 457, 1942.

360 Johnson, J. B. Management of Hemophilia, with Lyophile Human Plasma Intravenously Injected, *J A M A* **118** 799 (March 7) 1942.

361 Copley, A. L., and Lalich, J. J. The Influence of Blood Transfusion and Injections of Bursa Pastorens (Shepherd's Purse) Extract on the Clot Resistance in Two Hemophiliacs, *Am J M Sc* **204** 665, 1942.

362 Norcross, J. W. Hemophilia and Avitaminosis C. Report of a Case, *Lahey Clin Bull* **2** 219, 1942.

by administration of ascorbic acid and orange juice, with cessation of recurrent attacks of hemarthrosis. The coagulation time was not influenced by the vitamin C therapy, and it was suggested that the clinical improvement was related to increased capillary resistance.

The treatment of 32 patients for hemophilia with an extract of plant origin is reported by Hecht<sup>363</sup>. The exact source and chemical nature of this extract, called haemostypticum-Hecht, are not stated. It is said to be protein free and was nontoxic to animals into which it was injected. The clot formed in vitro after addition of the extract to hemophilic blood is similar to that of normal blood. In 12 patients in whom bleeding had been continuous for two to eight days, all hemorrhage ceased within ten minutes after intravenous administration of this agent. Used prophylactically before dental extraction and operative procedures in the nose and the throat, the substance prevented abnormal bleeding. Continuous therapy over a three year period was given to 2 patients with hemophilia, and they remained free from hemorrhage.

Hemophilia is a deficiency disease, according to Van Creveld,<sup>364</sup> who reports his experimental studies in support of this hypothesis. He feels that the absence of a plasma factor is responsible for the coagulation defect. A coagulation-promoting substance isolated from normal plasma by Van Creveld exerted a strong coagulating effect on hemophilic blood both in vitro and in vivo. This substance appears to be associated with the euglobulin fraction of plasma protein. It is practically absent from the plasma of a person with hemophilia but is found in the plasma of the parents of one afflicted with this disease. Van Creveld includes in the group of cases of sporadic hemophilia the isolated cases in which an extensive family history fails to reveal the disease in any of the patient's antecedents. To explain the occurrence of the disease in such circumstances one must assume either a mutation to the hemophilic trait or a latent inherited inclination to the disease carried through several generations without clinical manifestations. Three cases of sporadic hemophilia are presented, all with a prolonged coagulation time and with absence of the coagulation-promoting substance from the plasma.

A 43 year old man with a familial and a clinical history of hemophilia was studied by Lawrence and Johnson<sup>365</sup>. A circulating anticoagulant was demonstrated in his blood, and the coagulation time was only slightly decreased following a transfusion of blood. This patient's blood was transfused into a person known to have hemophilia, with subsequent prolongation of the coagulation time of the blood of the recipient. The authors feel that their patient had true hemophilia and that, in addition, his blood exhibited a circulating anticoagulant. The anticoagulant was neither heparin nor antithrombin. They suggest that further investigation be made with reference to the presence of a circulating anticoagulant in the blood of patients with hemophilia when the coagulation time is not appreciably shortened following transfusion of normal blood.

Tocantins<sup>366</sup> collected under special precautions the plasma of hemophiliacs and of normal persons. Following incubation, the plasma specimens were added to aqueous extracts of brain tissue. The hemophilic plasma decreased the thromboplastic activity of the tissue extracts far more than did the normal plasma. This

363 Hecht, E. Haemophilie. Eine neue Therapie, *Acta med Scandinav* **109** 177, 1941.

364 van Creveld, S. Sporadic Hemophilia and Pseudo-Hemophilia, *Acta pædiat* **29** 37, 1941.

365 Lawrence, J. S., and Johnson, J. B. Presence of Circulating Anti-Coagulant in Male Member of Hemophiliac Family, *Tr Am Clin & Climatol A* (1941) **57** 223, 1942.

366 Tocantins, L. M. Antithromboplastin in Hemophilia. Effect of Intravenous Injection of Hemophiliac's Own Thromboplastinized Plasma, *J Clin Investigation* **21** 646, 1942.

antithromboplastic activity of hemophilic plasma is suggested as the explanation of the delayed coagulation in hemophilic blood and the low thromboplastic content of citiated hemophilic plasma

Spontaneous hemothorax in a case of hemophilia is reported with roentgen studies by Pendergrass and Neuhauser<sup>367</sup> The authors state that although most forms of serosal hemorrhage are not infrequent in hemophilia, spontaneous hemothorax is generally unknown

An extensive review of therapy is given with ninety-seven references by Hecht<sup>368</sup> The diagnosis, the treatment and the theories as to the genesis of hemophilia are outlined by Hubbard<sup>369</sup>

The inheritance of a hemophilia-like condition in Poland China swine has been studied by Muhrer, Hogan and Bogart<sup>370</sup> They found that the characteristics of the bleeding abnormality in the swine closely fulfil the criteria set for the diagnosis of hemophilia The blood of the swine showed a prolonged coagulation time, a normal bleeding time and normal clot retraction The coagulation time of the recalcified plasma after either slow or rapid centrifugation was similar to that of hemophilic plasma The "bleeder" pigs had hemorrhages from minor abrasions, which frequently proved fatal Hemarthrosis was occasionally observed, according to Bogart and Muhrer<sup>371</sup> The trait is a simple recessive one and not sex linked Mertz<sup>372</sup> found the capillary resistance to negative pressure in the affected animals to range from 5 to 35 cm of mercury, with an average of 19 cm Animals in which the disease was absent gave values for capillary resistance of 35 to 60 cm of mercury, with an average of 51 cm Bleeding time as determined by the Duke method was consistently normal, but the saline bleeding time was found to be six times the normal value<sup>373</sup>

Copley and Lahch<sup>374</sup> produced a hemophilia-like condition in heparinized mice A prolonged coagulation time and a bleeding tendency were observed Irregular shape and retraction of clot and thixotropy, the property of becoming fluid when shaken and then again becoming solid, exhibited by certain gels, were observed

A proteolytic enzyme was obtained by Tagnon, Davidson and Taylor<sup>375</sup> from normal human plasma, with the property of lysing both fibrin and fibrinogen This enzyme, obtained by treating platelet-free, calcium ion-free plasma with chloroform, can change prothrombin to thrombin without the presence of calcium No prothrombin or fibrinogen was present in the enzymatic preparation, and the enzyme was found to be associated with the globulin fraction of the chloroform-

367 Pendergrass, E P, and Neuhauser, E B D Pleural Lesions in Hemophilia Report of a Case, *Am J Roentgenol* **48** 147, 1942

368 Hecht, E Hæmophilie Kritik der Therapie, *Acta med Scandinav* **109** 155, 1941

369 Hubbard, W E Hemophilia, *Nat Eclectic M A Quart* **33** 26, 1942

370 Muhrer, M E, Hogan, A G, and Bogart, R Defect in Coagulation Mechanism of Swine Blood, *Am J Physiol* **136** 355, 1942

371 Bogart, R, and Muhrer, M E Inheritance of a Hemophilia-Like Condition in Swine, *J Hered* **33** 59, 1942

372 Mertz, E T Anomaly of Normal Duke's and Very Prolonged Saline Bleeding Time in Swine Suffering from Inherited Bleeding Disease, *Am J Physiol* **136** 360, 1942

373 Mertz, E T Abnormal Capillary Resistance in Swine Suffering from an Inherited Bleeding Disease, *Am J Physiol* **138** 136, 1942

374 Copley, A L, and Lahch, J J Experimental Production of Hemophilia-Like Condition in Heparinized Mice, *Am J Physiol* **135** 547, 1942

375 Tagnon, H J, Davidson, C S, and Taylor, F H L Studies on Blood Coagulation A Proteolytic Enzyme Prepared from Calcium and Platelet Free Normal Human Blood Plasma, *J Clin Investigation* **21** 525, 1942



containing plasma When hemophilic plasma is treated similarly with chloroform, the enzyme obtained differs from that of normal plasma<sup>376</sup> This indicates, according to the authors, that in hemophilia the deficiency of a factor associated with the globulin fraction of plasma is paralleled by a deficiency of the proteolytic activity of the globulin fraction of chloroform plasma

*Telangiectasia*—Hereditary telangiectasis, according to Stellar,<sup>377</sup> has been reported in the literature in 550 members of 90 to 95 families to the end of 1930 He adds the case of a woman of 56 years in which recurrent epistaxis preceding the menses was present from puberty In later life gastrointestinal hemorrhage developed in this patient, and hemoglobin values below 10 per cent were recorded on four separate admissions to the hospital

Congenital afibrinogenemia was studied by Van Creveld<sup>364</sup> in the younger of twins By the method of analysis employed, no trace of fibrinogen could be demonstrated in the plasma A bleeding tendency and a prolonged coagulation time were manifest at the sixth week of age The elder twin was normal Necropsy revealed extensive hemorrhages into all body cavities The author also draws attention to the rare instance of the presence at an early age of a prolonged coagulation time, associated with a bleeding tendency that in later life disappeared with return of the coagulation time to normal

*Blood Platelets*—In 23 cases, after various operations, Shapiro, Sherwin and Gordimer<sup>378</sup> determined daily the number of platelets per cubic millimeter of blood, the coagulation time and the prothrombin time No change in the coagulation time was observed by the Lee and White method, but between the fifth and the fourteenth postoperative day an increase in the platelets occurred, attaining levels one and one-half to two times the previous values, with simultaneous lessening of the difference between the prothrombin times of undiluted and 25 per cent diluted plasma This change, which was observed in 14 of the cases, was evidently due to shortening of the prothrombin time of the diluted plasma In 3 cases the difference decreased to less than three seconds, with development of pulmonary infarction in 2 and thrombophlebitis in all These studies indicate that both the prothrombin and the thromboplastin of the blood increase in concentration or in activity in the postoperative period at the time when the incidence of postoperative thromboembolization is greatest

Wright<sup>379</sup> studied the stickiness of blood platelets following surgical operation and childbirth Serial observations of the platelet count and the stickiness revealed an increase in both beginning on the fourth postoperative or postpartum day and reaching a maximum on the tenth day The increased tendency of the platelets to adhere to surfaces was attributed to the appearance of young forms in the circulation Both the thrombocytosis and the greater adhesiveness of the platelets were suggested as contributing factors in the postoperative formation of thrombi

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376 Tagnon, H J , Davidson, C S , and Taylor, F H L Relationship of the Coagulation Defect in Hemophilia to a Plasma Proteolytic Enzyme, *J Clin Investigation* **21** 632, 1942

377 Stellar, L I Hereditary Telangiectasis Report of a Case, *New England J Med.* **226** 336, 1942

378 Shapiro, S , Sherwin, B , and Gordimer, H Postoperative Thromboembolization Platelet Count and Prothrombin Time After Surgical Operations, Simple Method for Detecting Reductions and Elevations of Prothrombin Concentration (or Activity) of Blood Plasma, *Ann Surg* **116** 175, 1942

379 Wright, H P Changes in the Adhesiveness of Blood Platelets Following Parturition and Surgical Operations, *J Path & Bact* **54** 461, 1942



The addition of heparin to dogs' blood in vitro resulted in a decrease in the platelet count, according to Copley and Robb<sup>380</sup>. Following intravenous administration of heparin to dogs,<sup>381</sup> an initial drop in platelets was followed by a rise. Lindelof<sup>382</sup> gave sulfapyridine to rabbits and observed no significant changes in the platelet counts, but after administration of sulfathiazole mild thrombopenia developed in these animals. Sonder<sup>383</sup> studied by means of the dark field the action of various anticoagulants on blood platelets and found that a 1 per cent solution of sodium oxalate exerted a damaging effect on them, whereas in a 2 per cent solution of sodium citrate the platelets remained in a quiescent state with little evident amoeboid motion. A solution designated as liquemin allowed observation of the dissolution of platelets and the formation of fibrin reticulum. Catel and Schotola<sup>384</sup> found that some samples of sesame oil when orally administered to normal persons raised the platelet count.

An indirect method of enumerating blood platelets on dried blood films, stained with brilliant cresyl while wet, is described by Pernokis<sup>385a</sup>. This is not a new method, it is described in the "Manual of Clinical and Laboratory Technic" by Weiss and Isaacs<sup>385b</sup>. Copley and Robb<sup>386</sup> demonstrated that the direct method of Vilarinho and Pimentel for counting thrombocytes is accurate and has the advantage that the count need not be performed immediately. It depends on separation of the platelets and the erythrocytes by centrifugation and preservation of the forms in a diluting fluid containing formaldehyde. A simplifying modification of the original technic is offered.

*Capillary Fragility*—The role of capillary integrity as a factor in the hemorrhagic diathesis receives increasing attention. Scarborough<sup>387</sup> believes that a substance (or substances) present in fruit, aside from ascorbic acid, is capable of increasing the resistance of capillary walls to negative pressure. The therapeutic efficacy of this substance, designated vitamin P, has not, as yet, been demonstrated. Higby<sup>388</sup> reviewed the literature dealing with the chemical nature of hesperidin and its experimental use as a source of vitamin P. Lindheimer, Hinman and Halliday<sup>389</sup> discussed clinical investigations with vitamin P. Cameron and Mills<sup>390</sup> administered this vitamin in a case of scurvy and found that the hemorrhagic manifestations of the disease were corrected promptly, but until vitamin C was added, the other aspects of the disease remained unchanged.

380 Copley, A. L., and Robb, T. P. Studies on Platelets. The Effect of Heparin on the Platelet Count in Vitro, *Am J Clin Path* **12** 416, 1942.

381 Copley, A. L., and Robb, T. P. Studies on Platelets. Effect of Heparin in Vivo on Platelet Count in Mice and Dogs, *Am J Clin Path* **12** 563, 1942.

382 Lindelof, S. A. J. Ueber den Einfluss einiger Sulfonamidpraparate auf den Gehalt des Blutes an Thrombozyten und weissen Blutkorperchen beim Kaninchen, *Upsala Lakaref forh* **47** 171, 1942.

383 Sonder, S. Der Einfluss verschiedener gerinnungshemmender Losungen auf die Evolutionsformen der Thrombozyten, *Helvet med acta* **8** 436, 1941.

384 Catel, W., and Schotola, H. Ueber den Einfluss des A-Vitamins und des Sesamols auf die Zahl der Blutplattchen, *Klin Wchnschr* **20** 1119, 1941.

385 (a) Pernokis, E. W. Simple Method of Evaluating Blood Platelets, *J Lab & Clin Med* **27** 1069, 1942. (b) Weiss, H. B., and Isaacs, R. Manual of Clinical and Laboratory Technic, Philadelphia, W. B. Saunders Company, 1940.

386 Copley, A. L., and Robb, T. P. Studies on Platelets. The Method of Vilarinho and Pimentel and a New Direct Method of Counting Blood Platelets, *Am J Clin Path* **12** 362, 1942.

387 Scarborough, H. Vitamin P, *Biochem, J* **33** 1400, 1939, Scarborough,<sup>325</sup> p. 408.

388 Higby, R. H. The Chemical Nature of Hesperidin and Its Experimental Medical Use as a Source of Vitamin P. A Review, *J Am Pharm A (Scient Ed)* **30** 629, 1941.

389 Lindheimer, G. T., Hinman, W. F., and Halliday, E. G. The Function and Occurrence of Citrin ("Vitamin P"), *J Am Dietet A* **18** 503, 1942.

390 Cameron, D. G., and Mills, E. S. Scurvy in Montreal, *Canad M A J* **46** 548, 1942.

Vitamin C administered as crystalline ascorbic acid did not alter capillary resistance as measured by negative pressure methods in normal subjects, according to Levcowich and Batchelder<sup>391</sup> Scarborough<sup>387</sup> states that he has never been able to increase capillary resistance with vitamin C except in special circumstances. He feels that the measurement of capillary resistance for the detection of subclinical scurvy is unjustified. Munro, Lazarus and Bell<sup>392</sup> determined capillary fragility for 182 medical students in England and compared the results with those for a group studied before the war. No significant difference was noted. Pignoli<sup>393</sup> found that the capillary resistance of normal women remained unaltered during the greater part of the menstrual cycle but that a slight decrease occurred in the last days of the old and the first days of the new cycle.

No change in vascular fragility as tested by negative pressure was observed by Schaefer<sup>394</sup> in patients with leukemia, anemia and polycythemia, but increased fragility was associated with infectious and inflammatory diseases and disorders of the vascular system.

Bell and his collaborators<sup>395</sup> compared the results obtained for 142 medical students by the negative suction method of Dalldorf and Russell with those obtained by the positive pressure test of Gothlin and found a low degree of correlation between them. From the results of one method it was impossible to predict the readings by the other procedure, nor was a conclusion reached as to which method of measuring capillary fragility was preferable. Each test proved consistent with itself.

Menkin<sup>396</sup> demonstrated that extracts of adrenal cortex and certain derived steroid fractions when administered to rabbits inhibited the increased permeability associated with inflammatory exudates. Observations made on capillary permeability in rabbits after injections of histamine were reported by Rigdon,<sup>397</sup> and observations on capillary permeability and inflammation in the skin of sensitized rabbits, by Rigdon and Haynes<sup>398</sup>. Zon, Ceder and Crigler<sup>399</sup> reported that administration of antiplatelet serum to rabbits prevents the normal increase of histamine in inflammatory lesions of the skin. Levy and Appleton<sup>400</sup> isolated from saliva a substance in crystalline form which increased capillary permeability. It is biologically similar to leukotaxine.

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391 Levcowich, T, and Batchelder, E L. Ascorbic Acid Excretion at Known Levels of Intake as Related to Capillary Resistance, Dietary Estimates, and Human Requirements, *J Nutrition* **23** 399, 1942.

392 Munro, H N, Lazarus, S, and Bell, G H. Capillary Fragility in Peace and War Statistical Comparison, *Lancet* **1** 648, 1942.

393 Pignoli, R. Capillary Fragility in the Meno-Metrorrhagies and Its Changes Following Treatment with Ascorbic Acid, *Ginecologia* **7** 85, 1941.

394 Schaefer, W. Untersuchungen über die Gefässerreisslichkeit bei internen Erkrankungen, *Ztschr f d ges exper Med* **108** 725, 1941.

395 Bell, G H, Munro, H N, Lazarus, S, and Scarborough, H. Capillary Fragility (Resistance), Negative- and Positive-Pressure Test Compared, *Lancet* **2** 536, 1942.

396 Menkin, V. Further Studies on Effect of Adrenal Cortex Extract and of Various Steroids on Capillary Permeability, *Proc Soc Exper Biol & Med* **51** 39, 1942.

397 Rigdon, R H. Observations on Effect of Histamine Phosphate on Capillary Permeability and Inflammation, *J Lab & Clin Med* **27** 1554, 1942.

398 Rigdon, R H, and Haynes, A. Observations on Capillary Permeability and Inflammation in the Skin of Sensitized Rabbits, *J Lab & Clin Med* **27** 598, 1942.

399 Zon, L, Ceder, E T, and Crigler, C. Presence of Histamine in Inflammatory Lesions, *Arch Path* **33** 452 (April) 1942.

400 Levy, B M, and Appleton, J L T. Effects of Saliva on Capillary Permeability, *J Dent Research* **21** 505, 1942.

*Hemostasis and Coagulants*—The mechanism of the coagulation of blood and of hemostasis is reviewed by Moore<sup>401</sup> and Hansen<sup>402</sup>. Lozner, Taylor and Taylor<sup>403</sup> investigated the so-called coagulation defect in menstrual blood and showed that the fluidity results from absence of both prothrombin and fibrinogen and that in effect the menstrual fluid is blood that has already undergone formation of clot and is therefore a suspension of formed blood elements and tissue debris in serum. It behaves similarly to defibrinated blood when added to solutions of thrombin, prothrombin and fibrinogen.

The lesions occurring in multiple sclerosis have been attributed tentatively to thrombosis of veins in the brain and the spinal cord. Exacerbation of the symptoms has been found to follow factors which some observers believe predispose to disturbance in the blood plasma secondary to thrombosis. Simon<sup>404</sup> studied the decrease in the blood coagulation time after the intravenous administration of typhoid vaccine and epinephrine in patients with disseminated sclerosis and patients with other diseases of the brain stem and spinal cord. After the injection of typhoid vaccine the clotting time of blood was reduced 25 per cent or more, and this change lasted three times longer in patients with multiple sclerosis. One patient was given a second dose of typhoid vaccine two weeks after the initial injection. The response of the clotting time was so much more intense and prolonged than initially that further studies were not attempted. The author suggests that in patients with multiple sclerosis there is a constitutional or an acquired sensitivity to stimuli which tends to reduce the blood coagulation time. Intensive or repeated stimulation of this hypersensitive mechanism under certain circumstances may lead to intravascular thrombosis.

The pharmacodynamics and the metabolism of oxalic acid are reviewed by Blain and Campbell<sup>405</sup>. A greater part of the one hundred and seventy-five articles published within the past decade appeared in foreign language journals. The intravenous administration of oxalic acid to rabbits was found to reduce the blood coagulation time by 44 per cent in fifteen minutes and by 54 per cent in one hour. Oxalic acid was given intravenously to 440 patients who had undergone a great variety of major operative procedures and produced either an immediate cessation of hemorrhage or a noticeable decrease in oozing in practically all cases. This material appeared to be most efficacious in controlling hemorrhage from large oozing surfaces. Between 20 and 40 mg administered intravenously proved to exert the optimal effect, and, if indicated, this amount could be given again in a short time. As a hemostatic agent oxalic acid proved safe, reliable, inexpensive and almost instantly effective. The use of oxalic acid in the treatment of hemophilia is reviewed in connection with that disease.

Tagnon and Taylor<sup>406</sup> administered a pseudoglobulin obtained from rabbit plasma orally to dogs, normal human subjects and to 2 patients with hemophilia.

401 Moore, C. V. Blood Coagulation and Hemostasis, West J Surg **50** 402, 1942

402 Hansen, H. L. Blood Coagulation and Hemostatic Agents, J Am Dent A **29** 673, 1942

403 Lozner, E. L., Taylor, Z. E., and Taylor, F. H. L. The So-Called "Coagulation Defect" in Menstrual Blood, New England J Med **226** 481, 1942

404 Simon, B. Blood Coagulation in Disseminated Sclerosis and Other Diseases of Brain Stem and Cord, Arch Neurol & Psychiat **48** 509 (Oct) 1942

405 Blain, A. W., and Campbell, K. N. Hemostatic Effect of Oxalic Acid. Clinical and Experimental Results, with Review of Literature, Arch Surg **44** 1117 (June) 1942

406 Tagnon, H. J., and Taylor, F. H. L. Effect on Coagulation Time of Oral Administration of Rabbit Thrombin, Proc Soc Exper Biol & Med **49** 32, 1942

A prompt fall in the coagulation time occurred in each instance. A gradual return to the preinjection level began two hours later.

Cunningham<sup>407</sup> noted that the application of sulfapyridine to experimental wounds exerted a hemostatic effect. Secondary and delayed tonsillar hemorrhages were controlled clinically by the application of sulfapyridine powder to the oozing surface. Sulfanilamide and sulfathiazole proved of little hemostatic value. Rutturk<sup>408</sup> found that hemostyphin, a lipid of unknown constitution prepared from animal phosphatides, reduced the bleeding time in rabbits when applied locally to cutaneous wounds. The hemostatic property of human milk was investigated by Hecht,<sup>409</sup> together with the role of ascorbic acid, in the physiology of coagulation. The influence on coagulation of dog plasma exerted by mother's milk was found to be independent of its content of vitamin C or of lipid phosphorus. The hemostatic property of milk was less active during the colostrum period than in the later stages of lactation. Extracts of the parotid gland of the toad *Bufo bufo*, used by Derouaux,<sup>410</sup> failed to exert any hemostatic action on the bleeding time of rabbits.

The clotting time of plasma in glass, paraffin, collodion, and lusteroid containers was investigated by Lozner, Taylor and MacDonald.<sup>411</sup> In a glass tube the plasma clotted in eleven minutes, in the other tubes, in from four to six times as long. Similar results were obtained with platelet-rich and with platelet-free plasma. If the plasma was first incubated in glass tubes and then added to hemophilic blood, the clot-promoting activity was two and a half times that of plasma incubated in the other three types of containers. The authors suggest that the "physiologic anticoagulant" responsible for the fluidity of circulating blood may be an attribute of the vascular endothelium which resembles physically such surfaces as collodion, paraffin and lusteroid. The experimental results indicate that a foreign surface acts by modifying some constituent of cell-free plasma. Platelet counts remained unchanged in citrated plasma exposed for one hour to the surface materials under study.

Schutz<sup>412</sup> reports studies of the influence of electric currents and electrically charged surfaces on blood coagulation. The clotting of fresh whole blood was observed to be delayed by weak direct currents and, depending on the metal used as the electrode, a variable effect was noted on the coagulation of the blood in contact with the electrodes.

Ferguson<sup>413</sup> studied an exceptionally stable prothrombin-free fibrinogen. On the basis of his observations, he feels that the formation of fibrin under the specific influence of thrombin is not related to denaturative and digestive phenomena. He offers a criticism of the theory of blood clotting incorporating such views

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407 Cunningham, B. P. Clinical and Experimental Studies with Sulfapyridine as Hemostatic Agent, *Ann Otol, Rhin & Laryng* **51** 301, 1942.

408 Rutturk, J. On Haemostyptics. Hemostyphin and Manetol, *Arch internat de pharmacodyn et de therap* **67** 305, 1942.

409 Hecht, E. Zur Kenntnis der Blutgerinnung. Vitamin C in der Blutgerinnungsphysiologie, *Acta med Scandinav* **109** 81, 1941.

410 Derouaux, G. Action du venin de crapaud sur le temps de saignement, *Arch internat de pharmacodyn et de therap* **66** 325, 1941.

411 Lozner, E. L., Taylor, F. H. L., and MacDonald, H. Effect of Foreign Surfaces on Blood Coagulation, *J Clin Investigation* **21** 241, 1942.

412 Schutz, F. On the Influence of Weak Electric Currents and Electrically Charged Surfaces on Blood Coagulation, *J Physiol* **101** 27, 1942.

413 Ferguson, J. H. Flocculation Maximum ( $p_H$ ) of Fibrinogen and Some Other Blood-Clotting Reagents (Relative Turbidimetry with Evelyn Photoelectric Colorimeter), *J Gen Physiol* **25** 607, 1942.

From normal dog plasma Tagnon<sup>414</sup> obtained an enzyme which possessed characteristics resembling those of trypsin. It lysed fibrinogen except in the presence of prothrombin, in the presence of the latter, coagulation intervened, followed by fibrinolysis. As the enzyme reacts with prothrombin to form thrombin without the intervention of calcium or thromboplastin, it was suggested that it plays a primary role in the normal coagulation of blood. Kaplan, Tagnon and collaborators<sup>415</sup> obtained from steer, swine and human plasma an enzyme capable of digesting fibrinogen, fibrin, gelatin and casein. This enzyme was absent in horse plasma.

A method for the quantitative measurement of the retraction of blood clots is offered by Aggeler, Lucia and Hamlin,<sup>416</sup> based on an estimation of the extracorporeal volume of the clot. After normal coagulation of the blood has occurred, the specimen is incubated for one hour at 37 C. The clot volume is obtained by subtracting the residual serum volume, after removal of the clot, from the total volume of the specimen. The difference between the percentage of the packed cell volume, obtained by centrifugation of a separate oxalated blood sample, and the percentage of the clot volume, is a measure of the extracorporeal volume of the clot. An average value of 9.1 per cent was obtained for 100 normal subjects, with a range of minus 5.9 to plus 24.1 per cent. The significance to be attached to variations in the extracorporeal volume of the clot is discussed by Lucia, Aggeler and Hamlin.<sup>417</sup> Diminished clot retraction was seen in hypoprothrombinemia and thrombopenia. However, similar results might occur when neither of these conditions is present, as in "thrombasthenia," fibrinogenopenia or "fibrinasthenia" or in the presence of a circulating inhibitor of clot retraction.

Hirschboeck and Coffey<sup>418</sup> measured the clot retraction time as the interval between the complete formation of the clot and the beginning of its separation from the sides of a glass container. This procedure was used<sup>419</sup> in 10 cases of pulmonary embolism, and retraction was found to begin in less than ten minutes in 9 instances. In the case of a normal person retraction begins in twenty-five to thirty minutes. The authors considered all postoperative patients with a clot retraction time of less than ten minutes as possible candidates for pulmonary embolism and suggested the use of this test as a guide to the selection of patients for prophylactic heparinization.

The tensile strength and the stretch of plasma clots were studied by Tarlov, Goldfarb and Benjamin.<sup>420</sup> The tensile strength of the plasma clots of persons who were ill was found to be greater than that of the plasma clots of normal persons. Lalich and Copley<sup>421</sup> use viscometer tubes in the determination of clot

414 Tagnon, H. J. The Significance of Fibrinolysis in the Mechanism of Coagulation of Blood, *J. Lab. & Clin. Med.* **27** 1119, 1942.

415 Kaplan, M. H., Tagnon, H. J., Davidson, C. S., and Taylor, F. H. L. Studies on Blood Coagulation. The Nature and Properties of a Proteolytic Enzyme Derived from Plasma, *J. Clin. Investigation* **21** 533, 1942.

416 Aggeler, P. M., Lucia, S. P., and Hamlin, L. M. Blood Clot Retraction. Measurement of the Extracorporeal Volume of the Clot, *J. Lab. & Clin. Med.* **28** 89, 1942.

417 Lucia, S. P., Aggeler, P. M., and Hamlin, L. M. Blood Clot Retraction. Significance of Extracorporeal Volume of Clot and Its Clinical Application, *Am. J. M. Sc.* **204** 507, 1942.

418 Hirschboeck, J. S., and Coffey, W. L., Jr. Method for Measuring Clot Retraction Time, *Arch. Path.* **33** 380 (March) 1942.

419 Hirschboeck, J. S., and Coffey, W. L., Jr. Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, *J. A. M. A.* **118** 1161 (March 28) 1942.

420 Tarlov, I. M., Goldfarb, A. I., and Benjamin, B. Method for Measuring Tensile Strength and Stretch of Plasma Clots, *J. Lab. & Clin. Med.* **27** 1333, 1942.

421 Lalich, J. J., and Copley, A. L. Study of Clot Firmness in Viscometer Tubes, *Proc. Soc. Exper. Biol. & Med.* **51** 235, 1942.

firmness Kershbaum and Schwartz<sup>422</sup> found that blood clots were nonpermeable to sulfonamide compounds in vitro and that neither heparin nor increased temperature induced permeability to such compounds. Bleeding time, lymph time and clot resistance were compared by Copley and Lalich<sup>423</sup>. After a clot had formed in a wound made by puncturing the skin with a mechanical lancet, a positive pressure of 100 mm of mercury was applied for three minutes to the limb above the site of the wound by means of a blood pressure cuff. Renewed bleeding was not observed in normal persons. In persons with hemophilia the application of the cuff renewed bleeding for as long as seventy-five minutes after the flow of blood had ceased. The author believes that the degree of stiffness of the clot and the ability of the clot to adhere to the skin are a measure of hemostasis.

*Dicoumarin*—The synthetic hemorrhagic agent 3, 3'-methylene-bis-(4-hydroxycoumarin), first isolated from spoiled sweet clover, has received extensive clinical trial during the past year. A review of the historical and experimental development of this compound is given by several authors<sup>424</sup>. Allen, Barker and Waugh<sup>424b</sup> used dicoumarin in 374 instances and found it a valuable agent in preventing intravascular thrombosis. The effect of dicoumarin seems to be on prothrombin only. The prolongation of prothrombin time indicates destruction of prothrombin, suppression of its action or inhibition of its formation. Dicoumarin, in addition to prolonging the prothrombin time, impairs clot retraction and accelerates the sedimentation of erythrocytes. After its administration, from twenty-four to forty-eight hours elapse before an effect on the prothrombin time is noted. On discontinuance of the administration of the material, the prothrombin time may be prolonged for two days to three weeks, depending on the amount given. The authors employed a dose of 300 mg of dicoumarin, given orally, on the first day and 200 mg on the second day. Thereafter, the 200 mg dose was repeated each day that the prothrombin time was less than thirty-five seconds as determined by Magath's modification of the Quick method. The importance of daily determinations of prothrombin as a guide to dosage and as a check on variations in effect on individual patients is stressed. Transfusions of fresh blood will temporarily reduce the prothrombin time. Vitamin K is ineffective.

In 69 cases of postoperative pulmonary embolism in which dicoumarin therapy was instituted, subsequent thrombosis or embolism developed in only 2. In neither of these instances was the prothrombin time sufficiently elevated to establish the adequacy of dicoumarin therapy. Untoward bleeding, classed as slight in 17, moderate in 9 and severe in 5, was encountered in 31 instances. Bleeding occurred most commonly from the operative site and was noted in 24 cases. Ecchymosis of the skin, hematuria, epistaxis and cerebral hemorrhage were also encountered. Two patients with subacute bacterial endocarditis who were receiving dicoumarin died. One showed signs of cerebral hemorrhage before death, and the other, extensive hemorrhages in many organs and tissues at necropsy. A tendency to bleed into the kidney or into the brain in bacterial endocarditis

422 Kershbaum, A, and Schwartz, L. Non-Permeability of Blood Clot to Sulfonamide Drugs in Presence of Increased Temperature, *Proc Soc Exper Biol & Med* **50** 165, 1942.

423 Copley, A. L., and Lalich, J. J. Bleeding Time, Lymph Time, and Clot Resistance in Man, *J Clin Investigation* **21** 145, 1942.

424 (a) Wright, I., and Prandoni, A. The Dicoumarin 3,3'-Methylene-Bis (4-Hydroxycoumarin). Its Pharmacologic and Therapeutic Action in Man, *J A M A* **120** 1015 (Nov 28) 1942. (b) Allen, E. V., Barker, N. W., and Waugh, J. M. A Preparation from Spoiled Sweet Clover (3,3'-Methylene-Bis [4-Hydroxycoumarin]) Which Prolongs Coagulation and Prothrombin Time of the Blood. A Clinical Study, *ibid* **120** 1009 (Nov 28) 1942. (c) Meyer, O. O., Bingham, J. B., and Axelrod, V. H. Studies on the Hemorrhagic Agent, 3,3'-Methylene-Bis (4-Hydroxycoumarin). The Method of Administration and Dosage, *Am. J M Sc* **204** 11, 1942.

is present without the administration of dicoumarin, and the authors feel that this agent is contraindicated in this disease

Meyer, Bingham and Axelrod<sup>424c</sup> administered dicoumarin to 73 patients, and except for a gross hemorrhage developing at the site of uterine curettage in 1, no toxic or untoward effects were noted. Studies of hepatic and of renal function were made in many instances while complete blood counts, a urinalysis, determinations of blood sugar and nonprotein nitrogen and Rumpel-Leede tourniquet tests were done in all cases. In no case was there observed a significant quantitative change in any test following the administration of dicoumarin. Prothrombin time and coagulation time were determined daily. The disodium salt of dicoumarin, was given intravenously, 4 Gm per kilogram of body weight, to 27 patients, and this treatment was repeated when indicated. A latent period of two to five days elapsed before the treatment attained maximal effectiveness, and no significant advantage of intravenous over oral administration was noted. An oral dose of 5 mg of dicoumarin per kilogram of body weight, followed by a daily dose of 1.5 mg per kilogram was given in 46 cases. It is imperative to measure the prothrombin and coagulation times daily to control individual variation in response.

Butsch and Stewart<sup>425</sup> warn that dicoumarin should be used with caution or not at all in cases in which an ulcerating or granulating lesion is present. They noted hematemesis following its administration in 2 of 4 cases of carcinoma of the stomach, 1 case terminated fatally. Debilitated and cachectic patients proved more susceptible to the effects of the drug.

Single oral doses of dicoumarin were given by Stats and Bullova<sup>426</sup> to 39 hospitalized persons. In 2 minor epistaxis developed, and 4 others came to necropsy. One showed unusual edema and intense hyperemia of the bronchi and a large quantity of hemorrhagic fluid within the bronchi. No lesions referable to dicoumarin were seen in the other 3 patients.

Vitamin K is reported by most authors as being ineffective in correcting the prothrombin time after administration of dicoumarin. Townsend and Mills<sup>427</sup> gave vitamin K to a patient while dicoumarin was still being administered and observed no further rise in the prothrombin or the coagulation time.

Dicoumarin synthesized in Sweden was used by Lehmann<sup>428</sup> in the treatment of 17 patients with thrombosis of the veins of the extremities. An oral dose of 0.75 Gm did not lower the prothrombin content of the blood as effectively as a similar dose administered to normal persons. The author<sup>429</sup> gave dicoumarin to lactating women and observed a lowering of the prothrombin content of the blood of both mothers and nursing infants. A preliminary report of the clinical use of dicoumarin in effectively prolonging the prothrombin and coagulation times is given by Le Fevre<sup>430</sup>.

425 Butsch, W. L., and Stewart, J. D. Clinical Experiences with Dicoumarin 3,3'-Methylene-Bis-(4-Hydroxycoumarin), *J. A. M. A.* **120** 1025 (Nov 28) 1942.

426 Stats, D., and Bullova, J. G. M. Effect of a Single Dose of 3,3'-Methylene-Bis (4-Hydroxycoumarin) upon Blood Coagulation in Humans, *Proc. Soc. Exper. Biol. & Med.* **50** 67, 1942.

427 Townsend, S. R., and Mills, E. A. The Effect of the Synthetic Haemorrhagic Agent, 3,3'-Methylene-Bis (4-Hydroxycoumarin) in Prolonging the Coagulation and the Prothrombin Time in the Human Subject, *Canad. M. A. J.* **46** 214, 1942.

428 Lehmann, J. Hypoprothrombinaemia Produced by Methylene-Bis (Hydroxycoumarin) Its Use in Thrombosis, *Lancet* **1** 318, 1942.

429 Lehmann, J. Hypoprothrombinemia Produced by 3,3'-Methylene-Bis (4-Hydroxycoumarin) and Its Use in the Treatment of Thrombosis, *Science* **96** 345, 1942.

430 Le Fevre, F. A. The Effects of 3,3'-Methylene-Bis (4-Hydroxycoumarin), (Dicoumarol) on the Prothrombin and Coagulation Times of the Blood. Preliminary Report, *Cleveland Clin. Quart.* **9** 147, 1942.



Prandoni and Wright<sup>431</sup> review and compare the modes of action and the indications for the use of heparin and dicoumarin. Heparin must be given intravenously, it is effective immediately after administration, and the duration of action is from one to four hours. Dicoumarin must be administered by mouth, it is not effective for twenty-four to seventy-two hours after the initial dose, but the average duration of its action is eleven days. A hemorrhagic syndrome was observed by the author in 8 patients who were receiving dicoumarin. In this group no single factor could be found responsible for the hemorrhagic complications. It was thought that individual susceptibility was in part responsible for the variations.

Hobson and Witts<sup>432</sup> state that misleading results are obtained if rabbit brain is used as a source of thromboplastin in the determination of prothrombin time after the administration of dicoumarin. They recommend either emulsions of fresh human brain or Russell viper venom with lecithin.

The employment of lusteroid tubes for the determination of the coagulation time of venous blood is suggested by Davidson and MacDonald<sup>433</sup>. An index of early changes in the coagulation of the circulating blood is obtained by this method which is not seen when glass tubes are employed.

Most laboratory animals dying from lethal doses of dicoumarin show hemorrhages in various organs and pulmonary edema, according to Rose, Harris and Chen<sup>434</sup>. Central necrosis of the liver was found in approximately one half of the rats and occasionally was seen in rabbits, mice and dogs that had died of intoxication with dicoumarin. Richards and Cortell<sup>435</sup> found some evidence of necrosis of the liver in dogs and monkeys after administration of dicoumarin. Guinea pigs on a vitamin C-free diet succumbed to the effects of dicoumarin sooner than animals on a diet rich in vitamin C. Baumann and collaborators<sup>436</sup> found that chlorobutanol and other substances which stimulate the synthesis of vitamin C in rats counteracted in part the hypoprothrombinemia produced by dicoumarin in these animals. The liver is thought to be the common site of origin for both prothrombin and vitamin C in rats, and similar proteins of the liver may be involved in the synthesis of each. However, the nature of these syntheses remains obscure. It is suggested that the activation of prothrombin might involve the action of vitamin C or of vitamin K or of both. Overman, Field, Baumann and Link<sup>437</sup> found that the administration of vitamin K to rats counteracted the hypoprothrombinemia when given before, during or twelve hours after the admin-

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431 Prandoni, A., and Wright, I. The Anticoagulants. Heparin and the Dicoumarin 3,3'-Methylene-Bis (4-Hydroxycoumarin), *Bull New York Acad Med* **18** 433, 1942.

432 Hobson, F. C. G., and Witts, L. J. Thromboplastin with Dicoumarin, *Brit M J* **1** 93, 1942.

433 Davidson, C. S., and MacDonald, H. An Evaluation of the Use of Dicoumarin, 3,3'-Methylene-Bis (4-Hydroxycoumarin), as an Anticoagulant, and Its Effect on Certain Plasma Constituents, *J Clin Investigation* **21** 644, 1942.

434 Rose, C. J., Harris, P. M., and Chen, K. K. Toxicity of 3,3'-Methylene-Bis (4-Hydroxycoumarin), *Proc Soc Exper Biol & Med* **50** 228, 1942.

435 Richards, R. K., and Cortell, R. Studies on the Anticoagulant 3,3'-Methylene-Bis (4-Hydroxycoumarin), *Proc Soc Exper Biol & Med* **50** 237, 1942.

436 Baumann, C. A., Field, J. B., Overman, R. S., and Link, K. P. Studies on the Hemorrhagic Sweet Clover Disease. Induced Vitamin C Excretion in the Rat and Its Effect on the Hypoprothrombinemia Caused by 3,3'-Methylene-Bis (4-Hydroxycoumarin), *J Biol Chem* **146** 7, 1942.

437 Overman, R. S., Field, J. B., Baumann, C. A., and Link, K. P. Studies on Hemorrhagic Sweet Clover Disease. Effect of Diet and Vitamin K on Hypoprothrombinemia Induced by 3,3'-Methylene-Bis (4-Hydroxycoumarin) in the Rat. *J Nutrition* **23** 589, 1942.



istration of dicoumarin Using rabbits, Overman, Stahlmann and Link<sup>438</sup> found that the simultaneous oral administration of menadione (2-methyl-1,4-naphthoquinone) and 1-ascorbic acid in high doses either drastically reduced or completely nullified the anticoagulant action of dicoumarin Similar results were obtained with menadione alone, but after the exclusive administration of 1-ascorbic acid only 15 of 50 rabbits were protected In doses sufficient to alleviate vitamin K deficiency menadione did not inhibit the anticoagulant action of dicoumarin Bollman and Preston<sup>439</sup> showed that in dogs large amounts of sulfathiazole failed to alter the effectiveness of dicoumarin Preexisting vitamin K deficiency, inanition, hepatic injury or renal injury exaggerated the prolongation of the prothrombin time McGinty and collaborators<sup>440</sup> gave purified beef prothrombin intravenously to dogs with lowered prothrombin levels as a result of previous administration of dicoumarin and observed a prompt rise in the concentration of plasma prothrombin The action of the injected prothrombin persisted for two to three days Studies on the plasma prothrombin time of rats, guinea pigs and dogs following the administration of dicoumarin are reported by Overman and his associates<sup>441</sup>

*Anticoagulants*—Methods for the assay of heparin are given by Seegers<sup>442</sup> and by Foster<sup>443</sup> Magerl<sup>444</sup> injected bacteria into heparinized rabbits and observed in the subsequent leukocyte response an increased percentage of lymphocytes and a decreased percentage of polymorphonuclear cells Heparin failed to inhibit the enhancing effect exerted on blood coagulation in vitro by certain strains of staphylococci, according to Rigdon and Haynes<sup>445</sup>

Sodium hexametaphosphate was shown by Caspe and Hadjopoulos<sup>446</sup> to be an effective anticoagulant for rabbits' blood both in vitro and in vivo

*Prothrombin and Vitamin K*—The clinical aspects of vitamin K therapy are reviewed by Smith and Warner<sup>447</sup> and the development and the chemistry of vitamin K compounds by MacCorquodale<sup>448</sup> The present concepts of the coagulation of blood with particular reference to the role of vitamin K are covered

438 Overman, R S, Stahlmann, M A, and Link, K P Studies on the Hemorrhagic Sweet Clover Disease The Effect of 2-Methyl-1,4-Naphthoquinone and L-Ascorbic Acid upon the Action of 3,3'-Methylene-Bis (4-Hydroxycoumarin) on the Prothrombin Time of Rabbits, *J Biol Chem* **145** 155, 1942

439 Bollman, J L, and Preston, F W The Effects of Experimental Administration of Dicoumarin 3,3'-Methylene-Bis (4-Hydroxycoumarin), *J A M A* **120** 1021 (Nov 28) 1942

440 McGinty, D A, Seegers, W H, Pfeiffer, C C, and Lowe, E R Plasma Prothrombin Concentration in Dogs Given 3,3'-Methylene-Bis (4-Hydroxycoumarin) and Purified Beef Prothrombin, *Science* **96** 540, 1942

441 Overman, R S, Stahlmann, M A, Sullivan, W R, Huebner, C F, Campbell, H A, and Link, K P Studies on the Hemorrhagic Sweet Clover Disease Effect of 3,3'-Methylene-Bis (4-Hydroxycoumarin) on the Prothrombin Time of the Plasma of Various Animals, *J Biol Chem* **142** 941, 1942

442 Seegers, W H The Quantity of Thrombin Required to Clot Heparin-Plasma Mixtures, *Proc Soc Exper Biol & Med* **51** 172, 1942

443 Foster, R H K The Assay of Heparin, *J Lab & Clin Med* **27** 820, 1942

444 Magerl, J F Ueber den Einfluss von Ultraviolett-Bestrahlungen auf die immunbiologische Wirksamkeit von Eigenblutinjektionen, *Ztschr f Immunitatsforsch u exper Therap* **99** 378, 1941

445 Rigdon, R H, and Haynes, A Observations on the Failure of Heparin to Inhibit Clotting of Blood in Vitro by Staphylococci, *Ann Surg* **116** 430, 1942

446 Caspe, S, and Hadjopoulos, L G Sodium Hexametaphosphate as Anticoagulant Preliminary Study, *Am J Pharmacol* **114** 175, 1942

447 Smith, H P, and Warner, E D Vitamin K Clinical Aspects, in Symposium on the Biological Action of the Vitamins, Chicago, University of Chicago Press, 1942, p 211

448 MacCorquodale, D W Vitamin K, in Symposium on the Biological Action of the Vitamins, Chicago, University of Chicago Press, 1942, p 202

by D'Alessandro,<sup>449</sup> who recommends that all patients undergoing surgical operation on the biliary tract have a prothrombin determination without regard to the presence or the absence of jaundice. Two brief reviews of the use of vitamin K are presented by Karabin<sup>450</sup> and Covintree.<sup>451</sup>

(a) *Hepatic Disease* The physiology of plasma prothrombin and its relation to disease of the liver are reviewed, and 117 references listed, by Andrus and Lord.<sup>452</sup> Abbott and Holden<sup>453</sup> studied 120 patients with hypoprothrombinemia before the oral administration of menadione and twenty-four to forty-eight hours later. In patients with severe hepatic damage little or no response to 8 mg of menadione was noted, while those with obstruction of the common duct practically always showed a rise in the prothrombin value. In patients with burns the response of the prothrombin time to administration of vitamin K was suggested as an early and accurate guide to prognosis. Allen and Julian<sup>454</sup> noted the response of the blood prothrombin to vitamin K therapy in 57 cases of obstructive jaundice and advanced disease of the liver. The prothrombin level rose to normal in twenty-four hours in every case of obstructive jaundice following either oral administration of 8 mg of menadione and 2.5 Gm of bile salts or parenteral injection of 10 mg of the water-soluble compound tetra-sodium 2-methyl-1,4-naphthoquinone diphosphoric acid ester (synkovite-Roche). In 31 instances of advanced disease of the liver the depressed prothrombin level was either not affected or elevated only slowly by similar therapy. Histologic observation of the livers of 17 patients coming to necropsy indicated no correlation between the extent of hepatic damage and either the initial response of the prothrombin level to vitamin K therapy or the rate or the degree of this response. The author concluded that deficiency of prothrombin is not a reliable measure of hepatic function, as it does not reflect the extent of hepatic damage. In a larger group of 42 patients Sweet, Lucia and Aggeler<sup>455</sup> found a fairly close clinical-pathologic correlation between hepatic damage and concentration of prothrombin in the plasma. In general, the value for prothrombin was normal by the Quick technic when there was little or no destruction of parenchymal tissue and was diminished with moderate or extensive destruction of the liver. In 2 cases deviation from this rule was noted, in the first, a case of extensive destruction of the liver from an infiltrating hepatoma, the concentration of prothrombin was 70 per cent of normal, and in the second, with only slight leukemic infiltration of the liver, the prothrombin content ranged from 40 to 20 per cent of normal. The authors felt that a better correlation occurred between the prothrombin time and the histologic appearance of the liver than between the former and the excretion of hippuric acid in Quick's test. Of the two tests, the concentration of prothrombin was thought to be the less sensitive indicator of hepatic function but the more accurate detector of destruction of hepatic parenchyma. One hundred unselected

449 D'Alessandro, A. J. Vitamin K and Its Role in Blood Coagulation, *Am J Surg* **57** 104, 1942.

450 Karabin, J. E. Vitamin K in Hypoprothrombinemia, *Illinois M J* **81** 56, 1942.

451 Covintree, G. E. Vitamin K, with Special Reference to Clinical Use, *Hahneman Monthly* **77** 83, 1942.

452 Andrus, W. deW., and Lord, J. W., Jr. The Physiology of Plasma Prothrombin and Its Relation to Liver Function, *Surgery* **12** 801, 1942.

453 Abbott, W. E., and Holden, W. D. Prothrombin Test as a Diagnostic and Prognostic Aid, *Arch Surg* **45** 261 (Aug.) 1942.

454 Allen, J. G., and Julian, O. C. Prothrombin and Hepatic Function, *Arch Surg* **45** 691 (Nov.) 1942.

455 Sweet, N. J., Lucia, S. P., and Aggeler, P. M. A Clinical-Pathologic Correlation Between Hepatic Damage and the Plasma Prothrombin Concentration, *Am J M Sc* **203** 665, 1942.

cases of disease of the liver and of the biliary tract encountered as routine diagnostic problems were studied by the Quick method of determining prothrombin by White, Deutsch and Maddock<sup>456</sup> The response of the hypoprothrombinemia to administration of vitamin K was compared as a test of hepatic function with the oral hippuric acid test, the fractional elimination of bromsulfalein and the excretion of urinary urobilinogen The correlation between the prothrombin time and the results of these tests for hepatic function was poor The excretion of hippuric acid proved a more reliable means of revealing hepatic insufficiency than did the prothrombin response to vitamin K therapy Abnormal excretion of hippuric acid was noted in 83 cases and an abnormal prothrombin level before and after therapy was seen in 53 The prothrombin level proved inferior to the other tests as a guide to prognosis A normal value for plasma prothrombin was misleading, but a depressed value was significant, and a failure to respond to vitamin K proved a progressively unfavorable sign Bleeding in the cases of hepatic cirrhosis encountered by these authors was due as frequently to ruptured varices as to a low level of prothrombin Stein<sup>457</sup> reports studies that confirm the rise in the blood prothrombin following parenteral injection of vitamin K in obstructive jaundice and the lack of this response in extensive disease of the liver Owen<sup>458</sup> states that when the administration of vitamin K is ineffective in correcting depression of the prothrombin level it may be reasonably assumed that there is impairment of hepatic function but that the prothrombin determination reflects pathologic changes in the liver only when the damage is extreme

Kapnick, Stewart and Lyons<sup>459</sup> measured hepatic function by the Quick method, the van den Bergh reaction and the bromsulfalein test in 68 patients who were receiving sulfanilamide derivatives During the course of the chemotherapy 14 patients showed an appreciable increase in prothrombin time, and several of these patients manifested abnormalities by the other tests No patient, however, showed an abnormal excretion of bromsulfalein or an increase of bilirubinemia without also showing a fall in prothrombin The severity of the infection appeared to be more significant as a cause of the depression of prothrombin than the type of drugs used, but the authors suggested that change in the prothrombin level may be used as an early indication of impending damage of the liver during therapy with sulfanilamide derivatives Definite deficiency of prothrombin was seen in 14 of 26 cases of disorders of the liver and biliary tract by Bechgaard<sup>460</sup> Quick's method as modified by Lehmann was recommended as an easy and reliable test for clinical use

The one stage method of Quick was compared with the two stage technique of determining prothrombin time in patients with hepatic disease by Ziffren, Owen, Warner and Peterson,<sup>461</sup> who found the latter procedure the more sensitive index

456 White, F W, Deutsch, E, and Maddock, S Comparison of Blood Prothrombin Levels with Standard Function Tests in Diseases of the Liver, *New England J Med* **226** 327, 1942

457 Stein, H B Distinction Between "Surgical" and "Medical" Jaundice by Effect of 2-Methyl-1,4-Naphthoquinone (Kapilin) on Plasma Prothrombin, *South African M J* **16** 12, 1942, Effects of 2-Methyl-1,4-Naphthoquinone on Clotting Factors of Blood of Jaundiced Patients with Hypoprothrombinemia, *South African J M Sc* **7** 72, 1942

458 Owen, C A Plasma Prothrombin An Index of Liver Function, *Harper Hosp Bull* **1** 113, 1942

459 Kapnick, I, Stewart, J D, and Lyons, C Plasma, Prothrombin and Liver Function During Sulfonamide Therapy, *New England J Med* **227** 944, 1942

460 Bechgaard, P Plasma Prothrombin and Vitamin K Deficiency in Diseases of Liver and Pancreas and in Diarrheas, *Ugesk f læger* **103** 1523, 1941

461 Ziffren, S E, Owen, C A, Warner, E D, and Peterson, F R Hypoprothrombinemia and Liver Function, *Surg, Gynec & Obst* **74** 463, 1942

of hepatic damage. Two patients in thyroid crisis were studied, and reduction of prothrombin was found in both instances.

(b) *Miscellaneous Disorders* The hemorrhagic tendency in sprue, due to hypoprothrombinemia, is believed by Alper<sup>462</sup> to result from a deficiency of intake, an increase of excretion and a failure of absorption of the fat-soluble vitamin K. The incidence of hypoprothrombinemia in certain tropical diseases is discussed by Diaz y Rivera and his associates,<sup>463</sup> who studied 12 patients with the hepatosplenic type of infection with *Schistosoma mansoni* and observed that, although 8 of them gave a history of hematemesis, no hemorrhagic tendency was apparent despite moderate prolongation of the prothrombin time. Page and Bercovitz<sup>464</sup> used a modification of the Quick method in studying the prothrombin of 21 patients with chronic ulcerative colitis. Six of the patients were found to have constant hypoprothrombinemia, and 13 had values fluctuating between normal and low levels. Eleven of these patients were found to have values for plasma fibrinogen slightly above normal.

Purpura due to deficiency of vitamin K in cases of anorexia nervosa was noted by Aggeler, Lucia and Fishbon,<sup>465</sup> who feel that the deficiency was due either to an exogenous dietary lack or to hypermotility of the gastrointestinal tract, although in no instance has hypoprothrombinemia been established to arise on the basis of purely functional disturbance of the intestinal tract.

Warner and Owen<sup>466</sup> used the two stage method of determining the prothrombin time in 20 cases of pernicious anemia, and found values below 50 per cent of normal in 10 and values of 75 per cent or more in only 3. Vitamin K was ineffective in altering the prothrombin level, but a rise occurred following the institution of liver therapy. Values determined by the Quick method were normal in all cases and were not modified by liver therapy. The reason for the difference in the results obtained by the two methods is not clear, but the prolongation of the prothrombin time as measured by the two stage method is not apparently related to the anemia or to its degree, and the response to liver therapy is confined to cases of pernicious anemia.

Levy<sup>467</sup> determined the bleeding time, the coagulation time, the prothrombin time and the degree of hepatic function in 60 cases of pulmonary tuberculosis. The Quick method and the bedside procedure of Smith revealed hypoprothrombinemia in 32 per cent of the patients, with the lowest values observed in those with pulmonary hemorrhage. In 14 patients experiencing pulmonary bleeding, varying in degree from streaked sputum to frank hemoptysis, the hemorrhage was promptly controlled by the administration of vitamin K. Serial determinations of prothrombin made on 12 tuberculous patients who had undergone thoracoplasty are reported by Savacool and Chodoff.<sup>468</sup> By the Quick technic a sharp drop was observed within one to two days after operation, with a lapse of one week or

462 Alper, J. M. The Hemorrhagic Tendency in Sprue, *Rev Gastroenterol* **9** 340, 1942.

463 Diaz y Rivera, R. S., Suarez, R. M., and Hernandez Morales, F. Hypoprothrombinemia Incident to Tropical and to Non-Tropical Diseases, *Bol Asoc med de Puerto Rico* **34** 177, 1942.

464 Page, R. C., and Bercovitz, Z. Prothrombin and Fibrinogen Studies in Chronic Ulcerative Colitis, *Am J Digest Dis* **9** 419, 1942.

465 Aggeler, P. M., Lucia, S. P., and Fishbon, H. M. Purpura Due to Vitamin K Deficiency in Anorexia Nervosa, *Am J Digest Dis* **9** 227, 1942.

466 Warner, E. D., and Owen, C. A. Hypoprothrombinemia in Pernicious Anemia, *Am J M Sc* **203** 187, 1942.

467 Levy, S. Vitamin K in Tuberculosis, with Special Reference to Pulmonary Hemorrhage, *Am Rev Tuberc* **45** 377, 1942.

468 Savacool, J. W., and Chodoff, R. J. Plasma Prothrombin in Tuberculous Patients. Effect of Surgical Collapse, *Am Rev Tuberc* **46** 432, 1942.

more before the preoperative level was regained. Vitamin K was ineffective in altering the hypoprothrombinemia of these patients, but a late spontaneous rise followed successful collapse therapy.

Dietz <sup>469</sup> reports that parenteral administration of vitamin K proved very effective in correcting menorrhagia and metrorrhagia. Schaad <sup>470</sup> used injections of vitamin K and of calcium in the successful treatment of a severe form of rheumatic purpura. Neither of these authors report determinations of prothrombin before or after vitamin K therapy.

(c) *Pregnancy and the Neonatal Period* The administration of soluble pentobarbital U. S. P. or of sodium amyl bromoallylbarbiturate as an analgesic during labor was found by Fitzgerald and Webster <sup>471</sup> to lower the prothrombin level in the blood of both mother and child. Vitamin K administered during labor prevented this fall and no neonatal hemorrhage was observed in 641 babies born of mothers so treated. A large number of infants born into families representing the lowest income group of a metropolitan area were studied by Parks and Sweet <sup>472</sup> for evidence of gross hemorrhage in the neonatal period. It was assumed that dietary deficiencies would be maximal in this group and that any procedure directed toward reduction of bleeding in the newborn should produce greatest benefits in such patients. On admission to the hospital in labor, the mothers of 1151 infants were given by mouth 5 mg of menadione, whereas another group consisting of the mothers of 1594 infants, received no vitamin K. Only severe hemorrhages, such as melena neonatorum, hematemesis, gross subcutaneous, cutaneous or definite intracranial hemorrhage or hemorrhage into the adrenal glands, were considered. The incidence of such bleeding was 1.4 per cent in the control group and 1.7 per cent in the infants whose mothers had received vitamin K.

The incidence of hemorrhagic manifestations in a group of 711 newborn babies who were given 1 mg of vitamin K orally as soon as they reached the nursery was compared with that in a control group of 982 infants by Sanford, Shmigelsky and Chapin <sup>473</sup>. All the infants were examined daily and determinations of prothrombin made by the Quick method for at least five consecutive days after birth. In the untreated newborn infants the prothrombin levels fell rapidly throughout the first, second and third days of life and rose abruptly during the fourth to seventh days before reaching a stationary level. In the infants given vitamin K immediately after birth, no decrease was observed in the prothrombin on the first or the second day of life. Except for a slight transient decline on the third day, the prothrombin values throughout the neonatal period were about 10 per cent above those of cord blood obtained at birth. The incidence of hemorrhagic manifestations was the same in the treated and the untreated group, amounting to 6.6 per cent. Conjunctival, vaginal petechial, cerebral and umbilical hemorrhage, melena and cephalhematoma occurred as many times in one group as in the other and the mortality percentage was the same for the two groups. The authors believe that the hemorrhagic manifestations noted differed from true hemorrhagic dis-

469 Dietz, R. Ueber die Wirkung von Vitamin K bei Meno-und Metrorrhagien, *Munchen med Wchnschr* **88** 1009, 1941.

470 Schaad, H. Vitamin K in einem schweren Fall von Purpura rheumatica, *Schweiz med Wchnschr* **71** 1622, 1941.

471 Fitzgerald, J. E., and Webster, A. Obstetric Significance of Barbiturates and Vitamin K, *J. A. M. A.* **119** 1082 (Aug 1) 1942.

472 Parks, J., and Sweet, L. K. Does Antenatal Use of Vitamin K Prevent Hemorrhage in the Newborn Infant? *Am J Obst & Gynec* **44** 432, 1942.

473 Sanford, H. N., Shmigelsky, I., and Chapin, J. M. Is Administration of Vitamin K to the Newborn of Clinical Value? *J. A. M. A.* **118** 697 (Feb 28) 1942.

ease of the newborn. In no instance was the coagulation time of whole blood increased beyond five minutes. The incidence of cerebral hemorrhage likewise was similar in the two groups, and the authors add that they have never observed cerebral hemorrhage in the newborn associated with hemorrhages elsewhere in the body or with prolongation of the whole blood coagulation time.

A review of the role of vitamin K in blood coagulation is given by Sage.<sup>474</sup> This author quotes Quick's comments on the paper of Sanford and collaborators. To call attention to the fact that hemorrhage in the newborn may occur from causes other than deficiency of prothrombin is a valuable contribution, in Quick's opinion, but Quick takes sharp issue with the authors if they are attempting to depreciate the use of vitamin K in preventing and treating hemorrhagic disease of the newborn. Waddell<sup>475</sup> takes the same view and states that vitamin K is efficient in the treatment and especially in the prevention of this dread disease of the newborn. In England, MacPherson and Henderson<sup>476</sup> and Capon<sup>477</sup> answer Sanford and associates in a similar vein.

Inasmuch as acute hypoprothrombinemia is the only condition of the newborn that responds to vitamin K, Kugelmass<sup>478</sup> feels that routine administration of this vitamin is wasteful in 99.5 per cent of infants so treated. If the latent hemorrhagic tendency present in the remaining 0.5 per cent becomes active, the rise in clotting time will indicate a decrease of available prothrombin, which then is a clear indication for vitamin K therapy. In a round table discussion of hemorrhage in the newborn Poncher<sup>479</sup> states that alterations in the walls of blood vessels constitute the most common cause of spontaneous bleeding in the neonatal period and that hypoprothrombinemia follows next in importance. In cases of spontaneous bleeding values below 20 per cent of the normal adult value when obtained by the Quick method are considered significant, but in the presence of vascular damage values ranging from 20 to 40 per cent of normal may play an important role in conditioning bleeding.

The increased incidence of hemorrhagic disease of the newborn in the winter and early spring is pointed out by Waddell,<sup>480</sup> and an identical seasonal increase in deaths from intracranial hemorrhage in the neonatal period has been found in the United States during a ten year period. Approximately one-third more infants died of this complication in the winter and spring months than during any other calendar month. Quick<sup>481</sup> feels that the incidence of intracranial hemorrhage is reduced and that other types of obscure bleeding, such as retinal, may be largely prevented by administration of vitamin K. The successful elevation of the prothrombin level of the newborn by administration of vitamin K to the mother or to the child is reported by Reiss and Schonberger.<sup>482</sup>

474 Sage, E. C. Clinical Evaluation of Vitamin K in Obstetrics, *Nebraska M. J.* **27** 314, 1942.

475 Waddell, W. W. Vitamin K for the Newborn, *J. A. M. A.* **118** 1389 (April 18) 1942.

476 MacPherson, A. I. S., and Henderson, J. L. Doubts on Vitamin K for the Newborn *Lancet* **1** 546, 1942.

477 Capon, N. B. Doubts on Vitamin K for the Newborn, *Lancet* **1** 602, 1942.

478 Kugelmass, I. N. Vitamin K for the Newborn, *J. A. M. A.* **118** 1389 (April 18) 1942.

479 Poncher, H. G. The Physiology of the Blood in the Newborn Infant, *J. Pediat.* **20** 637 1942.

480 Waddell, W. W., Jr. Hypoprothrombinemia and Hemorrhage in the Newborn Infant, *J. Pediat.* **20** 656, 1942.

481 Quick, A. J. Hemorrhagic Disease of the Newborn, *Marquette M. Rev.* **6** 160, 1942.

482 Reiss, W., and Schonberger, R. The Prothrombin Level in Newborn, as Influenced by Administration of Vitamin K to the Mother and to the Child, *Klin. Wchnschr.* **21** 319, 1942.

The effect of prelactation feedings on prothrombin deficiency in the newborn was studied by Richdorf and Kearney<sup>483</sup> In a group of infants given feedings of calcium caseinate or a 5 per cent solution of casein hydrolysate every four hours prior to the first breast feeding, the prothrombin level fell less than in infants starved for a similar twelve hour period after birth

The prothrombin time of the neonatal period was studied by MacPherson<sup>484</sup> in relation to the mother's dietary intake of vitamin K during pregnancy Uniformly low prothrombin times were found for children born of mothers whose diets were inadequate in green vegetables, milk, butter, meat, fats or cereals Four hydrocephalic infants were given at birth a diet consisting solely of dextrose and water On this vitamin K-free diet the infants showed an initial drop in prothrombin content comparable to that of normally fed newborn infants In contrast to normal infants, they showed a further fall in place of the expected rise in prothrombin usually seen This was considered by the author as evidence that the synthesis of vitamin K by the bacterial flora alone is insufficient as a source of supply to meet minimal physiologic requirements Spontaneous bleeding did not occur in these infants despite the fall of prothrombin at the end of ten days to levels which are usually associated with the onset of hemorrhagic disease in the newborn

Three newborn infants, one with atresia of the esophagus, a second with atresia and fistula from the esophagus to the bronchus and a third with complete obliteration of the gallbladder and the extrahepatic ducts, were followed during life with serial prothrombin determinations by Sanford and Shmigelsky<sup>485</sup> The first infant received fluids by injection but neither of the infants with atresia of the esophagus received food by mouth A prothrombin determination in the case of the first child on the fifth day of life was normal for a newborn infant but, owing to subsequent blood transfusion, no further tests were made in this case The second child gave a prothrombin curve identical with that of a normal newborn infant up to the time of death on the twelfth day In the third infant, with complete obliteration of the gallbladder and the extrahepatic ducts, a prothrombin level obtained on the eighth day of life corresponded closely to that of a normal newborn infant This child never received vitamin K bile salts or blood transfusions and at the age of 4 months had a prothrombin value of 95 per cent of normal by the Quick method The last determination made before the child's death at 6 months of age showed a drop to 75 per cent of normal By the two stage method, however, the plasma prothrombin was considerably below normal, ranging from 32 to 48 per cent, from the first to the sixth month of life The authors feel that these observations are not compatible with the view that the synthesis of vitamin K by bacteria from food in the small intestine demands the presence of bile for the conversion of vitamin K The liver may be the principal source of this vitamin, they suggest, and may continue to form vitamin K independently of an extrinsic supply until function of the liver is diminished by serious damage

483 Richdorf, L F, and Kearney, W Prothrombin Deficiency in the Newborn as Affected by Vitamin K and by Prelacteal Feeding, *Journal-Lancet* **62** 155, 1942

484 MacPherson, A I S Observations on the Aetiology and Prophylaxis of Prothrombin Deficiency and Haemorrhagic Disease in the Newborn, *J Obst & Gynaec Brit Emp* **49** 368, 1942

485 Sanford, H N, and Shmigelsky, I Is Presence of Bile and Food in Small Intestine Necessary for Formation of Prothrombin? Studies on Three Infants, One with Congenital Absence of Gallbladder and Extrahepatic Ducts and Two with Congenital Atresia of Esophagus, *Am J Dis Child* **63** 894 (May) 1942



Hypoprothrombinemia in congenital pyloric stenosis is discussed by Wallgren<sup>486</sup>. He reports that a hemorrhagic diathesis seen in this disease was successfully managed by administration of vitamin K.

Percutaneous administration of vitamin K was used by Vollmer, Abler and Altman<sup>487</sup> in the treatment of newborn infants. The speed of absorption appeared not inferior to that with oral administration and probably was superior to that with intramuscular injection of solutions in oil. The simplicity of this method of administration was hoped by the authors to lead to general use of vitamin K in the management of all newborn infants. Menadione, dissolved in a mixture of 80 parts liquid petrolatum and 20 parts kerosene so that 1 mg was contained in 0.1 cc of the solution, was applied in this approximate dose (4 drops) to the chest and proved safe and reliable in the prevention of physiologic hypoprothrombinemia of the newborn. A dermatitis resulting from topical application of 1 per cent menadione in an ointment base was noted in 5 of 9 adult patients by Page and Bercovitz<sup>488</sup>. Only after several applications did pruritus and erythema appear, and in 1 case chronic eczematoid dermatitis ensued. In a series of 24 newborn infants with whom this method was used, there was no evidence of contact dermatitis. The specially prepared ointment base was not responsible, as patch tests with the base alone were uniformly negative.

(d) Experimental Hypoprothrombinemia. Rats fed a diet containing a synthetic fat, largely dihydroxystearic acid, exhibited prolongation of clotting time, according to Lockhart, Sherman and Harris,<sup>489</sup> who found that addition of vitamin K to the diet prevented the development of this deficiency syndrome.

Evidence suggesting that the placenta is unusually sensitive to deprivation of vitamin K is presented by Moore and collaborators<sup>490</sup>. Rabbits were found to abort following ingestion of a diet deficient in vitamin K but adequately supplied with all other accessory factors, including vitamin E. Postmortem study showed retroplacental hemorrhages as the only evidence of a hemorrhagic diathesis. In these experiments the plasma prothrombin time did not reach levels usually indicative of critical hypoprothrombinemia.

Obstructive jaundice was produced experimentally in rabbits by Dyckerhoff and Marx,<sup>491</sup> who studied the prothrombin time and its response to the administration of vitamin K. Urnas,<sup>492</sup> by using a technic which practically eliminated trauma to the liver, excluded this organ from the circulation of cats and rats and observed in every instance rapid fall in the prothrombin level. The author either ligated the portal vein and the hepatic artery directly or first ligated the celiac artery and the mesenteric vessels to avoid stasis in the splanchnic region. The entire bowel except the duodenal stump, the common bile duct and the rectum were moved, thus leaving the liver in situ with the hepatic veins intact. The

486 Wallgren, A. Hemorrhagische Diathese bei kongenitaler Pylorusstenose (Hypoprothrombinämie), *Monatschr f Kinderh* **86** 32, 1941.

487 Vollmer, H., Abler, C., and Altman, H. S. Percutaneous Administration of Vitamin K, *Am J Dis Child* **64** 462 (Sept.) 1942.

488 Page, R. C., and Bercovitz, Z. Dermatitis from Topical Application of 2-Methyl-1,4-Naphthoquinone (Synthetic Vitamin K Analogue), *Am J M Sc* **203** 566, 1942.

489 Lockhart, E. E., Sherman, H., and Harris, R. S. Dihydroxy-Stearic Acid and Vitamin K Deficiency, *Science* **96** 542, 1942.

490 Moore, R. A., Bittenger, I., Miller, M. L., and Hellman, L. M. Abortion in Rabbits Fed Vitamin K Deficient Diet, *Am J Obst & Gynec* **43** 1007, 1942.

491 Dyckerhoff, H., and Marx, R. Ueber die Natur der hamorrhagischen Diathese bei Cholangie, *Biochem Ztschr* **311** 1, 1942.

492 Urnas, B. Plasma Prothrombin Level in Cats and Rabbits After Excluding Liver from Circulation, After Stimulation of Splanchnic Nerve and After Intravenous Injection of Adrenalin, *Acta physiol Scandinav* **3** 97, 1942.



animals survived only a few hours, but with evisceration alone no fall in plasma prothrombin occurred during a period of six to eight hours. By means of an Eck fistula, the portal blood was conveyed past the liver, and in animals thus prepared the prothrombin fell within two to four hours after operation and the decline was progressive until death ten to fifteen hours later. Transient increases in prothrombin were observed in cats under ether anesthesia after intravenous administration of epinephrine hydrochloride and after electrical stimulation of the splanchnic nerve.

The rare earths lanthanum, cerium and samarium were found by Vinche and Schmidt<sup>493</sup> to act as antiprothrombins, their effects being similar to those noted in previous studies with neodymium and praseodymium. Beaser, Segel and Vandam<sup>494</sup> injected the salts of the rare earths neodymium, lanthanum and cerium intravenously into rabbits and man. The clotting time could be prolonged to the point of incoagulability. Toxic manifestations consisting of chills, fever, cramps, hemoglobinemia and hemoglobinuria were observed. The authors concluded that these side effects rendered use of the salts as anticoagulants inexpedient.

(c) *Methods for Determining Prothrombin* The determination of the coagulation time of recalcified oxalated blood plasma is a simple and serviceable test for vitamin K deficiency, according to Cheney,<sup>495</sup> who points out that the tests for the prothrombin time advocated by others do not take into account the concentration of anticoagulant substances in the blood. The plasma coagulation time represents the resultant effect of the clot-promoting substances and the clot-retarding elements in a given plasma, and when an imbalance exists because of prothrombin deficiency, the clotting time is prolonged. Similar prolongation might occur with deficiency of thromboplastin, independent of vitamin K, but in clinical practice such a state occurs rarely and then only in the presence of severe thrombopenia. A standardized technic for determining the plasma coagulation time is presented.

By placing special emphasis on the difference between the prothrombin time of undiluted plasma and that of plasma diluted 25 per cent, certain abnormalities of the blood are revealed which are not shown by whole or by diluted plasma alone, according to Shapiro and collaborators,<sup>496</sup> who state that the absolute difference of the two determinations is a more reliable guide to prothrombin activity than either the prothrombin time of whole or that of diluted plasma alone. This conclusion was based on evidence that the difference between the prothrombin times of whole and diluted plasma varies inversely with the concentration or the activity of the prothrombin. Following administration of dicoumarin, a point is reached at which the prothrombin time of diluted plasma is substantially prolonged while that of undiluted plasma is only moderately extended. The determination of this difference is suggested as a useful procedure in the treatment of patients with dicoumarin as well as in the detection of the possible liberation into the circulating blood of an anticoagulant in certain other pathologic conditions. If dilution of these anticoagulant substances renders them ineffective, the prothrombin time of diluted plasma may be as short or even shorter than normal in spite of a lengthened prothrombin time of whole blood.

493 Vinche, E, and Schmidt, E. The Effects of the Rare Earth Salts on Prothrombin and Their Influence on Vitamin K<sub>2</sub>, *Ztschr f physiol Chem* **273** 39, 1942.

494 Beaser, S. B., Segel, A., and Vandam, L. The Anticoagulant Effects in Rabbits and Man of the Intravenous Injection of Salts of the Rare Earths, *J Clin Investigation* **21** 447, 1942.

495 Cheney, G. The Normal Plasma Coagulation Time, *Am J M Sc* **203** 325, 1942.

496 Shapiro, S., Sherwin, B., Redish, M., and Campbell, H. A. Prothrombin Estimation Procedure and Clinical Interpretations *Proc Soc Exper Biol & Med* **50** 85, 1942.

A detailed account of the technic of estimating prothrombin by the use of Russell's viper venom and lecithin in place of tissue thromboplastin extracts is given by Witts and Hobson,<sup>497</sup> together with the normal range of variation expected with this method. Witts<sup>498</sup> found that the difference between the coagulation times obtained with venom and with venom plus lecithin is inversely proportional to the number of platelets present in the plasma. A high difference with lecithin was noted in thrombopenia and thrombasthenia. In patients under dicoumarin therapy the difference with lecithin increases as the prothrombin is reduced. Further application of the difference with lecithin may serve as a method for the detection of inhibitor and accelerator substances in blood coagulation. Viper venom and lecithin are thought by Macfarlane<sup>499</sup> to be more reliable than animal tissue as a source of thromboplastin. The enzyme factor thrombokinase is supplied by the venom, and the lipid factor, present in animal thromboplastin, by lecithin. Page, de Beer and Orr<sup>500</sup> studied the method in 30 subjects and found that venom alone revealed certain prothrombin deficiencies not evident with lecithinized venom. The use of lecithinized venom offered a valuable adjunct, which may become more important as the difference between the two clotting times is better understood.

Current methods for estimating the prothrombin content of whole blood and plasma are reviewed by Warner.<sup>501</sup> The micro adaptations in use compare favorably in accuracy with the macro types of procedure. In cases of pernicious anemia in relapse or in cases of hepatic disease the results of the one stage method are not in agreement with those of the two stage technic. The two stage method has the advantage of eliminating the influence of factors which alter the speed of the conversion of prothrombin to thrombin.

Methods for performing microprothrombin determinations on whole capillary blood under standard physical conditions are described by Hoffman and Custer.<sup>502</sup> Other technics suitable for bedside prothrombin tests are described.<sup>503</sup>

(f) Substances Possessing Vitamin K Activity. The water-soluble tetra sodium salt of 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester was found by Davidson, Steigman and Udesky<sup>504</sup> to be more active on a molecular basis than menadione. By parenteral administration of it in 10 mg doses a satisfactory response was obtained in patients with hypoprothrombinemia in twenty-four to forty-eight hours. The toxicity of menadione and some related compounds was

497 Witts, L. J., and Hobson, F. C. G. Estimation of Prothrombin with Venom and Lecithin, *Brit. M. J.* **1** 575, 1942.

498 Witts, L. J. Disturbances in the Coagulation of the Blood (Finlayson Memorial Lecture), *Glasgow M. J.* **137** 57, 1942.

499 Macfarlane, R. G. Vitamin K and Estimation of Prothrombin, *Proc. Roy. Soc. Med.* **35** 410, 1942.

500 Page, R. C., de Beer, E. J., and Orr, M. L. Prothrombin Studies Using Russell Viper Venom. Effect of Lecithinized Venom on Prothrombin Clotting Time, *J. Lab. & Clin. Med.* **27** 830, 1942.

501 Warner, E. D. Current Methods for Estimating Prothrombin, *West. J. Surg.* **50** 408, 1942.

502 Hoffman, O. D., and Custer, R. P. A Micro Method for Determining Prothrombin Time on Fresh Capillary Blood Using Standard Physical Conditions, *Am. J. M. Sc.* **204** 420, 1942.

503 Lufkin, N. H., and Strolberg, M. A Simplified Prothrombin Test, *Am. J. Clin. Path. (Tech. supp.)* **6** 64, 1942. Abramson, D. J., and Weinstein, J. J. A Rapid Bedside Micro-Prothrombin Test, *ibid.* **6** 1, 1942. Ulin, A. W., and Barrows, E. A New Presumptive Test for Prothrombin Determination, *J. A. M. A.* **120** 826 (Nov. 14) 1942. Rhorer, A. A One-Minute Bed-Side Prothrombin Method, *Am. J. Clin. Path. (Tech. supp.)* **6** 51, 1942.

504 Davidson, M., Steigman, F., and Udesky, H. L. Clinical Studies on the Anti-Hemorrhagic Effects of a New Water-Soluble Vitamin K-like Substance, *Surg., Gynec. & Obst.* **74** 35, 1942.

investigated in animals by Ansbacher, Corwin and Thomas<sup>505</sup> An amount of menadione one hundred and twenty-five times the maximal clinical dose proved noninjurious even on repeated administration

Alcoholic extracts of European mountain ash berry (*Sorbus aucuparia* L.) proved effective in correcting abnormal clotting time in chicks with experimental hemorrhagic hypoprothrombinemia Shinowara, DeLor and Means<sup>506</sup> administered such an extract (soiparin) orally to 14 patients with biliary or hepatic disease and noted satisfactory elevations of the depressed prothrombin level in a majority of them, and symptomatic improvement when it was administered in conjunction with bile salts, beyond that ordinarily produced by other materials possessing vitamin K activity

Menadione, unlike vitamin K, when added to whole blood in vitro caused the formation of methemoglobin Scudi<sup>507</sup> found that menadione was rapidly converted to some other substance or substances which contained little of its original antihemorrhagic activity

In a group of mice with induced hypoprothrombinemia, Barnes<sup>508</sup> found that daily intraperitoneal injection of 0.1 cc of a 1 per cent solution of congo red over a period of three to eight days raised the plasma prothrombin level 23 per cent

Hypoprothrombinemia was induced in rats by a diet containing 20 per cent liquid petrolatum by Grodins and Ivy<sup>509</sup> When to these prothrombin-deficient animals 500 to 1,000 units of vitamin D was administered subcutaneously, elevation of the prothrombin level was observed in only a few cases The failure of vitamin D to alter hypoprothrombinemia in experimental animals has been reported by others

(g) Substances Possessing Thromboplastic Activity The thromboplastic activity of extracts of various tissues on the plasma of the same and different species of animals was studied by Copley<sup>510</sup> Thromboplastins were obtained from rabbit brain, rabbit skin, chicken brain and chicken skin A trend toward species specificity was noted in general and was seen in particular with chicken plasma Neither of the chicken thromboplastins exhibited any significant activity when tested with human plasma In human plasma the extract of rabbit brain accelerated the prothrombin time to a greater degree than the extract of rabbit skin

Instead of expressing the accelerating effect of the thromboplastin emulsion on the coagulation time of oxalated plasma in seconds, the authors introduce a "thromboplastic coefficient" This coefficient expresses the ratio of the coagulation time of recalcified plasma to the prothrombin time and gives a value of 1 if the added emulsion does not exhibit any activity During the course of the study it became apparent that the widely accepted explanation of the phenomena of the prothrombin time based on the Morawitz concept of blood coagulation could not be correlated with the present finding The discrepancy in the pro-

505 Ansbacher, S., Corwin, W. C., and Thomas, B. G. H. Toxicity of Menadione, Menadiol and Esters, *J. Pharmacol. & Exper. Therap.* **75** 111, 1942

506 Shinowara, G. Y., DeLor, C. J., and Means, J. W. Clinical and Laboratory Investigations on Extract of European Mountain Ash Berry, with Particular Reference to Its Anti-Hemorrhagic Activity, *J. Lab. & Clin. Med.* **27** 897, 1942

507 Scudi, J. V. Reactions of 2-Methyl-1, 4-Naphthoquinone (Menadione) with Whole Blood and Plasma in Vitro, *Proc. Soc. Exper. Biol. & Med.* **50** 16, 1942

508 Barnes, W. A. Effect of Congo Red on Plasma Prothrombin, *Proc. Soc. Exper. Biol. & Med.* **49** 15, 1942

509 Grodins, F. S., and Ivy, A. C. Effect of Vitamin D on Prothrombin Deficiency in the Rat, *Proc. Soc. Exper. Biol. & Med.* **49** 439, 1942

510 Copley, A. L. On the Thromboplastic Activity of Brain and Skin Extracts, *Am. J. Physiol.* **137** 178, 1942

thrombin time of the same plasma when various thromboplastins were employed and that between the prothrombin time and the simple coagulation time of recalcified plasma could not be explained by Quick's concept that the prothrombin time in seconds indicates the concentration of prothrombin present in the plasma. This explanation failed likewise when thromboplastins from different organs of the same species were utilized. Inasmuch as the contention that prothrombin is the precursor of thrombin is still in some doubt, it has been suggested by others that thromboplastin activates thrombin by exclusion of inhibitory substances. The latter view is incorporated by the author in the Howell theory of blood coagulation, in an effort to explain the discrepancies noted.

Mother's milk to which a small quantity of pyrrole has been added was used as a source of thromboplastin by Freudenberg<sup>511</sup> in determinations of prothrombin time.

(h) Miscellaneous Observations. A method for the quantitative measurement of antithrombin in blood was devised by Wilson<sup>512</sup>. Normal human plasma and serum contained similar amounts of antithrombin averaging 90 units per cubic centimeter when 1 unit is defined as that amount which will inactivate 1 unit of thrombin in four minutes at 28 C. The amount of antithrombin reported by this author is one thousand times greater than that observed with previous methods. During blood coagulation only a small portion of the thrombin is absorbed onto fibrin, the remainder being inactivated or neutralized by the antithrombic activity of the serum. In hypoprothrombinemia the presence or the absence of a hemorrhagic tendency is not fully explained on the basis of decreased prothrombin and variation in the conversion rate of prothrombin to thrombin. Normal human plasma contains 300 units of prothrombin per cubic centimeter, 1 unit being defined as that amount which when converted to thrombin will clot 1 cc of fibrinogen in fifteen seconds. In a patient with cirrhosis of the liver accompanied by spontaneous ecchymosis and bleeding of the gums, seen by the author, the plasma prothrombin was 25 per cent of normal, or 75 units per cubic centimeter, and the antithrombin was 95 units. When the prothrombin unitage approximates or is lower than the antithrombin unitage, a hemorrhagic diathesis will usually occur.

The prothrombin content of oxalated blood stores at 0 C was found stable for eight days by Laveigne and Laverne,<sup>513</sup> who determined the prothrombin content by diluting the plasma with fresh prothrombin-free plasma prior to employing the Quick technic. The authors felt that the prolonged clotting time obtained by other workers was influenced by a diminished fibrinogen content of the stored blood. The prothrombin content of dried plasma preserved in a frozen state and then reconstituted with distilled water was shown by Strumia<sup>514</sup> to be only 15 to 20 per cent of normal. However, if the plasma was reconstituted with distilled water saturated with carbon dioxide, values of 50 to 60 per cent were obtained, and if 0.1 per cent citric acid was used, the values were 67 per cent of normal. The original prothrombin content of the plasma, determined before drying, was found to be 65 to 70 per cent of normal. No untoward reactions in man have followed intravenous administration of plasma regenerated with 0.1 per

511 Freudenberg, E. Die Frauenmilchmethode zur Bestimmung der Prothrombinzeit, *Schweiz med Wchnschr* **71** 1256, 1941.

512 Wilson, S. J. Quantitative Studies on Antithrombin, *Arch Int Med* **69** 647 (April) 1942.

513 Laveigne, G. H. and Laverne, R. The Stability of Prothrombin in Stored Blood, *Compt rend Soc de biol* **136** 445, 1942.

514 Strumia, M. M. Preservation of Prothrombin in Dried Plasma, *J A M A* **119** 710 (June 27) 1942.

cent citric acid The excessive alkalinity of plasma reconstituted from the dried state is avoided, and deterioration of prothrombin is prevented, by the use of the citric acid solution The prothrombin activity of oxalated plasma was found by Tocantins<sup>515</sup> to fall rapidly after the plasma had been standing a few hours uncovered and exposed to air currents By aerating the plasma with carbon dioxide, the prothrombin activity could be restored to its initial value

#### BLOOD CHANGES ASSOCIATED WITH VARIOUS DISORDERS

*Blood in Infection*—The hematologic findings in 117 cases of appendicitis were analyzed by Dutton,<sup>516</sup> who concludes that a leukocyte count above 12,000 per cubic millimeter with 80 per cent neutrophils strongly suggests diffuse suppurative appendicitis and provides an indication for immediate surgical intervention Less marked leukocytosis and a lower percentage of neutrophils are compatible with a diagnosis of catarrhal inflammation When eosinophils are found in the stained blood film there is little likelihood that a suppurative process is present The author concludes that a diagnosis of acute appendicitis is apt to be inaccurate whenever studies of the blood demonstrate no abnormalities

After studying 250 assorted cases of arthritis Kling<sup>517</sup> concludes that the Weltman coagulation test does not possess the general utility of the erythrocyte sedimentation rate The latter he believes to be superior in evaluating the clinical course, although the Weltman procedure employed as an adjunct to the sedimentation rate and the differential count may yield helpful information

Lewis-Fanning and Myers<sup>518</sup> doubt that the sedimentation rate is altogether reliable in estimating the activity of a tuberculous process It is pointed out that the laboratory procedure to obtain this rate may occasionally give a result within normal limits in the presence of actively progressing lesions However, their studies indicate that in general the rate is of considerable prognostic value since the mortality rate of patients leaving the sanatorium with the erythrocyte sedimentation rate still elevated was considerably higher than that of the group who were discharged after the sedimentation rate had become normal

Lockie, Sanes and Vaughan<sup>519</sup> define Felty's syndrome as a chronic nonspecific arthritis of adults accompanied by splenomegaly and neutrophilic leukopenia The detailed postmortem observations in 1 case are reviewed Histologically, the enlarged spleen demonstrated sinus endothelial hyperplasia and infiltration by plasma cells and eosinophils, whereas sections of the liver showed parenchymatous degeneration and swelling of the Kupffer cells Other noteworthy findings were interstitial myocarditis, thyroiditis, pancreatitis and myositis The authors believe that these tissues demonstrated a nonspecific inflammatory reaction The inefficacy of all forms of therapy is emphasized Waitzkin's<sup>520</sup> patient derived temporary improvement following splenectomy In a case of Felty's syndrome presented by

515 Tocantins, L M Loss of Prothrombin Activity in Plasma Exposed to Air Current, *Proc Soc Exper Biol & Med* **49** 251, 1942

516 Dutton, L O Blood Findings in Acute Appendicitis, *Texas State J Med* **37** 669, 1942

517 Kling, D H The Weltman Coagulation Reaction and the Sedimentation Test in Arthritis, *Ann Rheumat Dis* **2** 256, 1941

518 Lewis-Fanning, E, and Myers, M Prognostic Value of the Blood Sedimentation Rate in Pulmonary Tuberculosis, *Brit M J* **2** 125, 1942

519 Lockie, L M, Sanes, S, and Vaughan, S L Chronic Arthritis Associated with Neutrophilic Leukopenia, Splenomegaly and Hepatomegaly "Felty's Syndrome," *Am J Clin Path* **12** 372, 1942

520 Waitzkins, L Felty's Syndrome, *Virginia M Monthly* **69** 80, 1942

Stenberg<sup>521</sup> splenectomy was performed after all conservative measures had failed to control the anemia. Improvement of the blood occurred, but the arthritis did not recede. Elsom and Ingelfinger<sup>522</sup> report their findings in 2 patients both of whom had eosinophilia of the blood, pneumonitis and laboratory findings compatible with chronic brucellosis.

Brumpt<sup>523</sup> points out that a parasite of rats, *Hepatozoon*, is exclusively phagocytosed by monocytes and that white blood cell counts of infected animals have shown the monocytes ranging from 35 to 85 per cent. The author suggests that the experimental use of this parasite might lead to a better understanding of the origin and development of the monocyte. Fatal hemolytic anemia of pigeons caused by *Plasmodium relictum* (a parasite of birds resembling that causing malaria) is reported by Hill<sup>524</sup>.

*Nephritis*—Anemia as seen in 36 children with nephritis is analyzed by MacArthur<sup>525</sup>. The group consisted of 21 children with acute nephritis, 5 with the nephrotic syndrome, 5 with nephrosclerosis (chronic interstitial) and 5 with chronic hemorrhagic nephritis. Only in those with chronic hemorrhagic nephritis was true anemia found. It was characterized by an orthochromic, normocytic blood picture with a normal or slightly increased number of reticulocytes and associated mild leukocytosis. Iron therapy was without effect on the anemia. The author believes that the anemia is not due to hypoplasia of the bone marrow, for it is not associated with diminution of the number of white blood cells or of that of reticulocytes. In the absence of complicating hemorrhage, no anemia was found in the children with nephrosclerosis. In the children with the nephrotic syndrome, hemoconcentration reached its maximum during the period of oliguria, but slight anemia was occasionally present. In the children with acute nephritis hemoconcentration was at its height during active diuresis. Our experience indicates that in advanced glomerular nephritis with azotemia, and occasionally in nephrosclerosis with absolute renal insufficiency, selective impairment of erythropoiesis occurs, the block appearing very early in the development of the red blood cells. Only in this sense can the resulting anemia be designated as hypoplastic. In patients with nephrosis, mild to moderate anemia, often macrocytic, may be attributable to alterations in protein metabolism.

*Chemical Intoxications*—Eleven hundred and four workers employed in the rubber industry were studied by Wilson<sup>526</sup>. They were exposed to benzene fumes, the concentration averaging 100 parts per million. Seven and five tenths per cent showed slight blood changes, and 2.2 per cent more pronounced changes. Of the latter group consisting of 25 persons, 9 were hospitalized, 3 of these died. The blood changes resulting from exposure to benzene fumes can be summarized as leukopenia with increase in the ratio of monocytes and decrease in the polymorphonuclear cells. The red cell count, the hemoglobin content and the platelet count were low. Aspirated marrow showed varying degrees of hypoplasia. The blood prothrombin level remained normal. The treatment recommended by the author consists of multiple small blood transfusions and infusions of 2 to 5 cc of yellow bone marrow. Multiple vitamin therapy with intramuscular injections

521 Stenberg, C. L. The Value of Splenectomy in Felty's Syndrome, *Ann Int Med* **17** 26, 1942.

522 Elsom, K. A., and Ingelfinger, F. J. Eosinophilia and Pneumonitis in Chronic Brucellosis. A Report of Two Cases, *Ann Int Med* **16** 995, 1942.

523 Brumpt, E. Monocytose parasitaire du rat. Son utilisation possible pour l'étude de la monocytopenie, *Compt rend Soc de biol* **136** 345, 1942.

524 Hill, C. M. Anemia as a Cause of Death in Bird Malaria, *Am J Hyg* **36** 143, 1942.

525 MacArthur, P. Anaemia in Nephritis, *Arch Dis Childhood* **17**.1, 1942.

526 Wilson, R. H. Benzene Poisoning in Industry, *J Lab & Clin Med* **27** 1517, 1942.

of liver extract, together with oral administration of iron, calcium and phosphorus, is suggested

Meyer and Ginsberg<sup>527</sup> report fatal aplastic anemia following exposure to benzene fumes. Prior to death of the patient three unsuccessful attempts were made to obtain sternal marrow. Postmortem observations are reported. An aplastic marrow was revealed.

The expected blood findings in lead poisoning are discussed by Kehoe<sup>528</sup>. The red cell count is likely to be decreased and perhaps low, but may be entirely normal. The hemoglobin value may show similar variations, but no characteristic change is noted in the white cell count. In most cases a significant increase in the number of stippled red blood cells in the peripheral blood is noted. The mean number of stippled cells in the blood of normal persons is given as  $339.18 \pm 9.72$  per million red blood cells. In 30 cases of lead poisoning studied before the subsidence of an acute attack, an average of 5,856 stippled red blood cells per million was found, with a range of 720 to 16,000. In the course of an acute illness the absence of stippled red blood cells can usually be taken as convincing evidence that lead is not the responsible agent, but an exception to this rule is seen in sudden overwhelming lead intoxication. Due to the wide variation of the individual hemopoietic response to plumbism, the number of stippled red cells cannot be taken as an index to the degree of absorption of lead. A progressive increase in the stippled cells, however, is evidence of increasing intoxication by lead. On recovery from plumbism the stippled cells disappear before the concentration of lead in the blood and in the urine has returned to normal.

Matz<sup>529</sup> reports lead poisoning in a 20 month old child following the use of a plaster of lead oleate in the treatment of infantile eczema.

Increased numbers of stippled red blood cells were found by Abraham and Baird<sup>530</sup> while they were examining blood films for malaria at an army post. Investigation led to the discovery that tetraethyl lead gasoline was being used for cooking in a mess kitchen. Five of 7 men exposed to the fumes were found to excrete abnormal amounts of urinary lead. Clinical symptoms of lead intoxication developed in 2 of the 5 men, while 3 remained symptom free. The men in whom plumbism developed were cooking in a closed kitchen. In other groups, cooking with tetraethyl lead gasoline outdoors under a tent fly, no signs of lead intoxication appeared.

The origin of porphyrinuria in lead poisoning was studied by Kark and Meiklejohn<sup>531</sup>. The type III coproporphyrin found in the urine in plumbism has been shown to differ from the type I porphyrin which is present in several other conditions associated with porphyrinuria. This has led to the assumption that the porphyrin in lead poisoning, which is similar to the protoporphyrin of hemoglobin, is present as a consequence of alteration in the metabolism of hemoglobin. The authors gave solutions of hemoglobin intravenously to 2 patients with lead poisoning. The plasma bilirubin showed a rise resembling closely that observed

527 Meyer, L. M., and Ginsberg, V. Aplastic Anemia, *J. Indust. Hyg. & Toxicol.* **24** 37, 1942.

528 Kehoe, R. A. Symposium on Industrial Medicine. Lead Absorption and Lead Poisoning, *M. Clin. North America* **26** 1261, 1942.

529 Matz, M. H. Lead Poisoning Caused by Plaster of Lead Oleate, Diachylon. Report of a Case Occurring During the Treatment of Infantile Eczema, *Arch. Pediat.* **59** 805, 1942.

530 Abraham, A. E., and Baird, J. A. Clinical and Subclinical Lead Intoxication, *War Med.* **2** 450 (May) 1942.

531 Kark, R., and Meiklejohn, A. P. Significance of Porphyrinuria in Lead Poisoning, *J. Clin. Investigation* **21** 91, 1942.



in normal persons, accompanied by a transient increase in urinary urobilinogen. No detectable increase in the excretion of porphyrin resulted in either the urine or the feces. The authors felt that the porphyrin observed in lead poisoning was not derived from abnormal destruction of red cells but might originate from defective synthesis of hemoglobin. The stippled red blood cells have been shown by others to contain protoporphyrin. The present authors suggest that the stippled cells are the result of faulty synthesis of hemoglobin with resulting accumulation of porphyrin in the erythrocytes. When the stippled cells are ultimately destroyed, the porphyrin, being an abnormal metabolite, is excreted in an abnormal manner. Kench, Gillam and Lane<sup>532</sup> take a different view of the origin of porphyrinuria in lead poisoning. They measured the amount of protoporphyrin in the blood of 12 subjects whose exposure to lead had been moderately heavy. The amount of pigment was insignificant compared with the quantity anticipated if the existing anemia was dependent on failure of iron-porphyrin formation. One of the authors ingested 20 mg of lead acetate daily for thirty-eight days, and although urinary coproporphyrin type III reached high values the concentration of hemoglobin in the blood remained unaltered. Further, no relation was found between the degree of stippling and the concentration of protoporphyrin in the blood. The diminution in the formation of hemoglobin in plumbism, the authors suggest, is due not to nonutilization of protoporphyrin but to depression of marrow function as a result of intoxication by lead.

An excellent review of the clinical and blood changes associated with poisoning in munition workers is presented by Noro<sup>533</sup>. The blood dyscrasias following exposure to amatol (a mixture of trinitrotoluene and ammonium nitrate) and tetryl (tetranitromethylamine) were found to be similar. One hundred and nine patients were studied, and anemia, normochromic or hyperchromic, was found in 43, leukopenia in 22 and leukocytosis in 13. The white cell count ranged from 2,600 to 20,300 per cubic millimeter. Thrombopenia was noted in 50 patients and thrombocytosis in 6. Poisoning following use of mercury fulminate produced anemia with a high color index and a remarkable degree of thrombocytosis, the platelet count reaching 1,240,000 per cubic millimeter in 1 instance.

No direct relation between synthesis of porphyrin and metabolism of hemoglobin was demonstrated by Bjorkman,<sup>534</sup> who produced experimental lead poisoning in rabbits. He feels that porphyrinuria has its origin in a disturbance in the metabolism of cytochrome. Bambach, Kehoe and Logan<sup>535</sup> report that 90 per cent of the total amount of lead in the blood of rabbits is found in the cellular portion after separation of the corpuscles by centrifugation.

The symptoms of chronic acetanilid poisoning are reviewed by Austin,<sup>536</sup> who reports the case of a 44 year old woman with chronic anemia and leukopenia due to combined acetanilid and aminopyrine poisoning. The total white cell count never exceeded 3,000 per cubic millimeter over a four year period of observation. Progressive neutropenia and splenomegaly were noted. On withdrawal of the

532 Kench, J. E., Gillam, A. E., and Lane, R. E. Hemopoiesis in Lead Poisoning, *Biochem J* **36** 384, 1942.

533 Noro, L. Investigation of Trotyl, Tetryl and Fulminate of Mercury Poisoning in Munition Workers in Finland, *Acta med Scandinav (supp)* **120** 1, 1941.

534 Bjorkman, S. E. Coproporphyrinuria and Hemoglobin Metabolism in Experimental Lead Poisoning, *Acta med Scandinav* **108** 568, 1941.

535 Bambach, K., Kehoe, R. A., and Logan, M. A. The Plasma-Cell Partition of Blood Lead, *J Pharmacol & Exper Therap* **76** 326, 1942.

536 Austin, V. T. Chronic Anemia and Leukopenia in Combined Acetanilid and Aminopyrine Poisoning, *J A M A* **120** 911 (Nov 21) 1942.



aforementioned drugs, the blood values returned to normal and the spleen was no longer palpable. In this patient leukopenia and neutropenia followed oral administration of either aminopyrine or acetanilid. A positive intradermal test was obtained with specially prepared aminopyrine.

#### METHODS AND MISCELLANEOUS MATERIAL

Quantitative studies on all of the corpuscular elements of the blood of healthy young men are reported by Hamre and Au.<sup>537</sup> The group comprised 137 boys and men between the ages of 15 and 25 years who were residents of the Hawaiian Islands. This is the most comprehensive study of the blood values of a large group of normal persons which has been published. No age or racial differences were noted in these values, and the values reported agree closely with those which have been obtained in other parts of the world. Hicks<sup>538</sup> determined the hemoglobin and erythrocyte levels of 125 infants within twelve hours after birth, excluding those who were delivered prematurely. The observed range of the hemoglobin was 16.1 to 27.2 Gm. per hundred cubic centimeters, with a mean of 22.3 Gm. and a standard deviation of 2.77 Gm. The red cells ranged between 4,650,000 and 9,670,000 per cubic millimeter, with a mean of 6,950,000 and standard deviation of 950,000. The author found no correlation between the hemoglobin values and the birth weights of the infants studied. Unfortunately, he gives no information concerning a possible relation between the length of time after delivery before the cord was tied and the concentration of erythrocytes and of hemoglobin.

In order to find out whether routine determination of hemoglobin, of packed cell volume of erythrocytes, of mean corpuscular hemoglobin concentration and of sedimentation rate would yield information of sufficient clinical significance to warrant permanent establishment of such a service in a large general hospital, Sturgis and Bethell<sup>539</sup> carried out these procedures for almost all of the adults registering at the University Hospital, Ann Arbor, Mich., during a two week period. The blood specimens were collected with a minimum of stasis in tubes containing the dry ammonium and potassium oxalate mixture of Heller and Paul. 2 mg. of the combined salt for each cubic centimeter of blood. The hemoglobin was determined by an oxyhemoglobin photoelectric method, calibrated with the oxygen capacity method of Van Slyke, the sedimentation rate was measured by the Wintrobe and Landsberg method, Wintrobe tubes being used, in which the packed cell volumes were later determined by centrifuging at 3,000 revolutions per minute for thirty minutes. Minimum normal hemoglobin values for men and women were established respectively, as 13.3 and 12.1 Gm. per hundred cubic centimeters. The maximum normal sedimentation for both sexes, "corrected" to a hematocrit value of 47 per cent, was assumed to be 10 mm. in one hour. Determinations were made for 763 persons including some healthy ones, who were being examined before employment. The total percentage of abnormally low hemoglobin values was 24.26. Hypochromia, characterized by a mean corpuscular hemoglobin concentration of less than 30 per cent, was indicated by the blood values of 72.4 per cent of the anemic patients. The sedimentation rates of 48.4 per cent of the subjects exceeded 10 mm. per hour and those of 33.1 per cent 15 mm. per hour. This survey has now been established on an annual

537 Hamre, C. J., and Au, M. H. Hematologic Values for Normal Healthy Men Sixteen to Twenty-Five Years of Age, *J. Lab. & Clin. Med.* **27**: 1231, 1942.

538 Hicks, J. D. Haemoglobin Values in the Blood of New-Born Infants, *M. J. Australia* **2**: 117, 1942.

539 Sturgis, C. C., and Bethell, F. H. The Determination of Hemoglobin, Sedimentation Rate and Packed Volume of Erythrocytes as a Routine Procedure at the Time of Hospital Registration, *Univ. Hosp. Bull., Ann Arbor* **8**: 101, 1942.

basis, and data obtained from the examination of about 20,000 subjects will be reported at a later date

Bruckmann <sup>540</sup> determined the hemoglobin concentration of blood drawn from the vein, the ear and the finger for healthy and for anemic persons. The values obtained on blood from the finger and the vein agreed closely, whereas those secured on blood from the ear were significantly higher

Hematologic values of normal male rats, including the erythrocyte count, the hemoglobin value, the reticulocyte percentage, the leukocyte count and the differential formula, are reported by Thewlis and Meyer,<sup>541</sup> with a statistical analysis of the data. Kindred <sup>542</sup> estimated for 8 young male rats the volume and the number of cells per unit volume of bone marrow, spleen, thymus, lymph nodes and Peyer's patches, together with the percentage distribution of the different types of cells, the percentage in mitosis, the rate of growth and the rate of destruction. He draws the conclusion that the myeloid elements are adequate for the maintenance of normal numbers of granulocytes but that the erythroid tissue is insufficient to account for the circulating erythrocytes and the needs of replacement unless one accepts the theory of Jordan that small lymphocytes may undergo transformation into erythroblasts

Clegg and King <sup>543</sup> point out that circulating hemoglobin may be divided into two parts: (1) reduced hemoglobin and oxyhemoglobin and (2) carboxyhemoglobin and methemoglobin or sulphemoglobin. A satisfactory method of determination should measure both portions. The author reports the use of an alkaline hematin method which accomplishes this purpose. Specially prepared hemin is employed as a standard, and the method was found to be rapid, convenient and accurate. Rimington <sup>544</sup> describes a method for the determination of hemoglobin in which all of the heme pigments in the blood are converted to pyridine-hemochromogen and the concentration of this substance measured in a photometer. Pure solutions of heme are readily prepared and serve as the basis for the standard. Flink and Watson <sup>545</sup> also employ a pyridine-ferrohemochromagen method in the determination of hemoglobin and related heme pigments in blood plasma, feces and urine. The error in recovery of added hemoglobin for urine and plasma was within 10 per cent, for feces recovery ranged between 75 and 95 per cent. The authors point out that protohematin and deuterohematin are not included in the heme pigments which are converted to pyridine-hemochromogen

Duffie <sup>546</sup> has devised a pocket-sized visual photometer for the estimation of hemoglobin. An illuminant is mounted in the base of the instrument and a green filter no. 74, is placed above the solution of oxyhemoglobin and the permanent sliding neutral gray standard. Color comparison is eliminated by this rapid and practical method, since the readings are based on the concentration of light passing through the green filter

540 Bruckmann, G. Blood from the Ear Lobe. Preliminary Report, *J. Lab. & Clin. Med.* **27**: 487, 1942

541 Thewlis, E. W., and Meyer, O. O. Blood Count of Normal White Rats, *Anat. Rec.* **82**: 115, 1942

542 Kindred, J. E. A Quantitative Study of the Hemopoietic Organs of Young Adult Albino Rats, *Am. J. Anat.* **71**: 207, 1942

543 Clegg, J. W., and King, E. J. Estimation of Haemoglobin by the Alkaline Haematin Method, *Brit. M. J.* **2**: 329, 1942

544 Rimington, C. Haemoglobinometry, *Brit. M. J.* **1**: 177, 1942

545 Flink, E. B., and Watson, C. J. A Method for the Quantitative Determination of Hemoglobin and Related Heme Pigments in Feces, Urine and Blood Plasma, *J. Biol. Chem.* **146**: 171, 1942

546 Duffie, D. H. Elimination of Color from Visual Hemoglobinometry, *J. A. M. A.* **119**: 493 (June 6) 1942

According to Ponder,<sup>547</sup> neither acid nor alkaline hematin methods of estimating hemoglobin agree well with Wong's non method. The errors of the hematin methods depend on the variable periods required for complete conversion of hemoglobin, and on substances other than hemoglobin in both plasma and cells which affect the color of the solution.

The total volume of circulating erythrocytes as determined with the aid of radioactive iron-tagged cells is not increased by the administration of epinephrine to human subjects, according to Ross and Chapin,<sup>548</sup> although they observed rises in the venous hematocrit values and the plasma protein concentration of from 4 to 6 per cent. These changes were attributed to hemoconcentration or to redistribution of cells and plasma in the vascular system.

A method of estimating the average length of life of the red cells in the circulation of rabbits is reported by Graam.<sup>549</sup> This procedure is based on inducing reticulocytosis by means of hemorrhage and determining the time which elapses between the reticulocyte peak and the secondary fall in the erythrocytes. By this method the author determined a duration of life of erythrocytes of six to seven days in young rabbits and about five days in older animals.

The changes in size of erythrocytes occurring after hemorrhage were measured by Brown and his associates,<sup>550</sup> who found minor increases after a single large hemorrhage, still smaller increases after several severe hemorrhages and no increase after repeated withdrawals of small amounts of blood. They observed no evidence indicating that swollen red cells are immobilized in the capillaries of muscles after hemorrhage or that such cells are returned to the circulation following plasma transfusion as previously described by Brennan. The authors' observations, made after single large hemorrhages in 13 human subjects, after operation in 9 cases and in 1 rabbit and 2 cats, indicated that hemodilution is complete in about twenty-four hours in normal subjects but that it may be prolonged for from three to four days after operation.

A method for determining the approximate surface area of the erythrocyte is described by Bernstein and Chesluk.<sup>551</sup> The procedure is based on the assumption that the erythrocyte is a flat disk rather than a biconcave structure, but by construction of a rectangle the error introduced by this assumption is largely compensated for. By this method the mean surface area of the erythrocytes of normal subjects averaged 135.44 square microns with a standard deviation of 3.517 square microns.

Cytologic changes in polymorphonuclear neutrophils occurring in toxic conditions are described by Ponder and Ponder.<sup>552</sup> Such changes include ameboid outline of the cell, toxic granules and vacuoles in the cytoplasm, and pyknotic areas in the nucleus. A method is devised for the qualitative grading of each cell which, according to the authors, clearly reflects the clinical condition of the patient and is more informative than the total leukocyte count, the neutrophil

547 Ponder, E. Errors Affecting the Acid and the Alkali Hematin Methods of Determining Hemoglobin, *J Biol Chem* **144** 339, 1942.

548 Ross, J. F., and Chapin, M. A. The Absence of Erythrocyte Reserves in Human Subjects as Indicated with Radioactive Tagged Cells, *J Clin Investigation* **21** 640, 1942.

549 Graam, D. G. The Average Length of Life of the Red Corpuscle, *J Lab & Clin Med* **27** 448, 1942.

550 Brown, G. L., Miles, J. A. R., Vaughan, J. M., and Whitby, L. E. H. The Effect of Haemorrhage upon Red Cell Size and Red Cell Distribution, *Brit M J* **1** 99, 1942.

551 Bernstein, M., and Chesluk, H. M. The Surface Area of the Human Erythrocyte, *J Lab & Clin Med* **27** 1280, 1942.

552 Ponder, E., and Ponder, R. V. The Cytology of the Polymorphonuclear Leucocyte in Toxic Conditions, *J Lab & Clin Med* **28** 316, 1942.

percentage, the nuclear shift or the degenerative index. E. Ponder<sup>553</sup> describes two types of neutrophils, the "polycyte" and the "propolycyte," in relation to the typical neutrophil, on the one hand, and the macropolycyte on the other. "Polycytes and their precursors, propolycytes, are characterized by hypersegmentation or complex nuclei, but are of usual size." Such forms are believed to result from an increase in the rate of maturation of the neutrophil series, and when seen in the course of an acute or chronic infection, are of favorable prognostic significance.

The granules of eosinophilic leukocytes have been made the subject of an investigation by Buña<sup>554</sup>. According to him, such granules have been believed to consist of lipids (Mosler, Pappenheim), proteins (Weiss), lipoprotein complexes (Fiessinger) and hemoglobin (Weidenreich). Barker and Petry state that the granules of the eosinophils of horse blood contain 11 per cent of iron, a finding which has been challenged by Marwedel and Askanazy. Liebereich has classified the granules of the eosinophils into two groups: (1) the A granules, which are soluble in acetic acid, (2) the A' granules, which are resistant to acetic acid, are basophilic and stain by the Ziehl-Neelsen technic. Buña applied the Ziehl-Neelsen method of staining to sections of human and pig tissue, fixed in 10 per cent solution of formaldehyde and embedded in paraffin, and demonstrated that the granules of the eosinophils are not only acid fast but also alcohol fast. The acid-fastness is a relative quality, since the granules are decolorized by prolonged treatment with nitric acid in a dilution of 1:3. He found varying degrees of acid-fastness in the granules of eosinophils, as well as in several other tissue elements. This gradient of acid-fastness he considers quite different from the sharp distinction between the A and A' granules of Liebereich. Buña also studied the chemical composition of the eosinophil granules by means of microincineration and found that they do not contain iron.

Dark field illumination in the study of stained blood possesses two chief advantages over the bright field technic, according to Ralph<sup>555</sup>. In the first place, structures which otherwise are not seen are rendered visible and resolvable, and, in the second, greater ranges of size, refractivity and color are obtained, permitting a more detailed differentiation of cell types.

A method for determining blood volume in dogs with the aid of radioactive phosphorus is described by Brown, Hempelmann and Elman<sup>556</sup>. In principle it is the same as that employing radioactive iron, but it possesses technical advantages. The authors enumerate the superiorities of cell over plasma methods of determining blood volume, namely: Plasma is not so delimited anatomically as cells, changes in vascular permeability may affect results when plasma is measured, dyes introduced into the blood stream may diffuse out of the plasma or may be excreted. Chapin and Ross<sup>557</sup> believe that the hematocrit method of determining cell volume gives values which are too high. They state that the true cell volume may be determined by dilution of dye T 1824 or by dilution of plasma proteins. Values obtained in this way consistently average 8.5 per cent lower than hemato-

553 Ponder, E. The Polycyte, *J. Lab. & Clin. Med.* **27** 866, 1942.

554 Buña, W. Sobre reacciones de las granulaciones de los leucocitos eosinofilos, *An. Fac. med. de Montevideo* **27** 93, 1942.

555 Ralph, P. H. The Use of Darkfield Illumination for the Study of Stained Blood Films, *Stain Technol.* **17** 7, 1942.

556 Brown, F. A., Jr., Hempelmann, L. H., Jr., and Elman, R. The Determination of Blood Volume with Red Blood Cells Containing Radioactive Phosphorus (P32), *Science* **96** 323, 1942.

557 Chapin, M. A., and Ross, J. F. Determination of True Cell Volume by Dye Dilution, by Protein Dilution, and with Radioactive Iron. Error of Centrifuge Hematocrit, *Am. J. Physiol.* **137** 447, 1942.

crit values for cell volume. Results obtained by the use of radioactive non-tagged erythrocytes agreed with those secured by the dye and plasma protein dilution methods.

Sternal marrow obtained by aspiration may yield cultures of typhoid bacilli when both blood and fecal cultures are negative, according to Sprenger<sup>558</sup>. Twelve cases are reported. The author states that positive results from culture of sternal marrow are not limited to any special period of the illness.

The anemia of flexed tail mice is due to the inheritance of a recessive gene, and the anemia itself conditions the associated skeletal and developmental changes, according to Gruneberg<sup>559</sup>. He describes the anemia as of normocytic, hypochromic type, but the data suggest that macrocytosis persists for a longer period after birth in the anemic mice than in the healthy controls. The author states that pathologic cell development is confined to the early embryonic and extramedullary mode of hemopoiesis. This type of blood cell formation is the sole form of hemopoiesis until the sixteenth day of gestation, and normally it is replaced by the definitive medullary type of erythropoiesis at the time of birth or soon thereafter, but in the anemic mice it persists for about two weeks after birth and ceases by the beginning of the third week. The pathologic erythrocytes formed in this persistent abnormal hemopoiesis survive in the circulation for at least two but not for longer than six weeks. With their final disappearance, the red cell picture of the flexed tail mice becomes entirely normal, but during the transition period between the two modes of erythropoiesis cells of intermediate grades of abnormality are observed in the circulating blood.

The factors governing the sedimentation of erythrocytes have been made the subject of an extensive study, reported in a series of articles, by Nichols<sup>560</sup>. The work includes a survey of the literature on the subject, with a bibliography of 347 references. For his own determinations the author employed horse blood, the Wintrobe tube, Heller and Paul's dry oxalate mixture as an anticoagulant and a photographic recording device.

According to Whittington and Miller,<sup>561</sup> the sedimentation velocity is mainly a function of the agglutination power of the plasma, and the kinematic viscosity of the plasma acts as an extremely sensitive index of its agglutinating power. Therefore, the determination of the viscosity and the specific gravity of the plasma should give information which is analogous to that provided by the measurement of the sedimentation rate. The mathematical concepts which enter into these relationships are discussed, and experimental studies are reported.

The phenomenon of erythrocyte sedimentation is reviewed by Della Vida,<sup>562</sup> who advocates that the test be performed within four hours after the blood has been obtained and that the dry ammonium and potassium oxalate mixture of Heller and Paul be used as an anticoagulant. He prefers a tube 200 mm in length with a diameter of 2.5 mm and states that only the rate of fall during the

558 Sprenger, K. Die sternal Punktion als diagnostisches Hilfsmittel beim Typhus abdominalis, *Klin Wchnschr* **26** 284, 1941.

559 Gruneberg, H. The Anemia of Flex-Tailed Mice (*Mus musculus* L.) Static and Dynamic Haematology, *J Genetics* **43** 45, 1942.

560 Nichols, R. E. A Study of the Phenomenon of Erythrocyte Sedimentation. I A Critical Survey of the Literature, *J Lab & Clin Med* **27** 1317, 1942, II The Establishment of a Reliable Measurement of the Phenomenon—Its Reproducibility and Limitations, *ibid* **27** 1410, 1942, III Anticoagulation as a Technical Source of Variations, *ibid* **27** 1569, 1942, IV Venous Stasis, Delay, Temperature of Sample, Containers, Agitation, and Quantity of Formed Elements as Sources of Technical Variations, *ibid* **28** 75, 1942.

561 Whittington, R. B., and Miller, A. K. Haemomechanics and Sedimentation Rates, *Tubercle* **23** 195, 1942.

562 Della Vida, B. L. The Sedimentation Rate and the Sedimentin Index, *Brit M J* **2** 278, 1942.

period of constant settling should be recorded. Corrections for anemia are made by the use of the "sedimentin index" of Day.

Kopp<sup>563</sup> found no absolute correlation between the plasma concentration of fibrinogen or albumin, the albumin-globulin ratio or the globulin-fibrinogen ratio, on the one hand, and the corrected sedimentation rate, on the other. The sedimentation rate was usually increased when the globulin fraction of the plasma was elevated, regardless of the content of fibrinogen. The author's studies were carried out on 5 male patients undergoing fever therapy for dementia paralytica. He employed the Rouike and Ernstene method of determining the sedimentation rate. The electrophoretic patterns and the sedimentation rates of normal and of pathologic bloods were compared by Shedlovsky and Scudder,<sup>564</sup> who obtained a correlation between the alpha globulin level and the sedimentation rate that was at least as good as the correlation involving the fibrinogen level.

The sedimentation rates of healthy young persons between 11 and 17 years of age are reported by Roche, Stannus and Isberg.<sup>565</sup> The subjects comprised 60 boys and 40 girls, all residents of Miami Beach, Fla. The Rouike and Ernstene method was employed, and the values of 75 per cent of the subjects ranged between 0.09 and 0.65 mm.

The return of the sedimentation rate to normal closely paralleled the clinical recovery from acute glomerulonephritis and could be correlated with changes in the Addis count, according to Rubin, Rapoport and Waltz.<sup>566</sup> Hertz, Ringler and Bernstein<sup>567</sup> were unable to confirm the conclusion of Koster and of Feldman that blood from patients with cancer exhibits an acceleration of sedimentation which persists for twenty-four hours or longer after its withdrawal. They conclude that this test is of no value in the differentiation of cancerous from non-cancerous conditions.

Teleoentgenograms were made in 32 cases of severe anemia by Gupta.<sup>568</sup> In all but 2 cases there was some increase in the transverse diameter of the heart above the predicted normal. An inverse relation occurred between the hemoglobin content and the cardiac enlargement, but the greatest hypertrophy was found in cases of "hyperchromic" anemia. With improvement of the anemia, a regression of the size of the heart occurred in 95 per cent, although a certain amount of enlargement persisted even after the anemia had been corrected.

Choked disks were observed by Watkins, Wagener and Brown<sup>569</sup> in 4 patients with various types of blood dyscrasia in whom no evidence of a related intracranial lesion was found. Two had thrombopenia purpura. One had severe anemia following recurrent hemorrhage from a gastric ulcer. It was suggested that the papilledema was produced in these instances by local tissue anoxia due to loss of blood.

563 Kopp, I. The Relationship of the Plasma Proteins to the Corrected Sedimentation Rate, *J Lab & Clin Med* **27** 1072, 1942.

564 Shedlovsky, T., and Scudder, J. A Comparison of Erythrocyte Sedimentation Rates and Electrophoretic Patterns of Normal and Pathological Human Blood, *J Exper Med* **75** 119, 1942.

565 Roche, C. F., Stannus, D. G., and Isberg, E. M. Erythrocyte Sedimentation Rate Determinations on Normal Youths, *J Lab & Clin Med* **28** 297, 1942.

566 Rubin, M. I., Rapoport, M., and Waltz, A. D. A Comparison of Routine Urinalysis, Addis Count, and Blood Sedimentation Rate as Criteria of Activity in Acute Glomerulonephritis, *J Pediat* **20** 32, 1942.

567 Hertz, J. J., Ringler, S. H., and Bernstein, H. Is the Maintained Sedimentation Rate Specific for Malignancy? *J Lab & Clin Med* **28** 323, 1942.

568 Gupta, P. C. Study of the Size of Heart in Cases of Severe Anemia Occurring in the United Provinces of Agra and Oudh in India, *Indian J M Research* **30** 129, 1942.

569 Watkins, C. H., Wagener, H. P., and Brown, R. W. Cerebral Symptoms Accompanied by Choked Optic Disks in Types of Blood Dyscrasia, *Am J Ophth* **24** 1374, 1941.

## Book Reviews

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**A Guide to Practical Nutrition** Edited by Michael G Wohl, M D, and John H Willard, M D, for the Committee on Nutrition and Deficiency Diseases Price, not given Pp 98 Philadelphia Philadelphia Medical Society, 1943

These brief articles summarize well current views on nutrition They are pleasantly written by men who know the subject, some of national reputation One wonders, however, whether there is really need for so many books on food and vitamins The subject has been publicized from every possible quarter, lay and professional literature is readily available There are ponderous treatises, as well as the kindergarten type of syllabus for the ordinary citizen, who (it is presumed) needs a childish approach

It would seem reasonable in times like these, when economy is important, that additional books on nutrition should contribute something really new This is hardly the case with the present compendium

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## News and Comment

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### GENERAL NEWS

**Mississippi Valley Medical Society**—The ninth annual meeting of the Mississippi Valley Medical Society will be held at Quincy, Ill, September 29 and 30 The program for the meeting will be practical and will be keyed to wartime medicine All ethical physicians are invited to attend Medical officers of the Army and Navy are cordially invited to, be guests of the society if they register in service uniform A detailed program of the meeting may be obtained from the secretary, Dr Harold Swanberg, 209-224 W C U Building, Quincy, Ill

**Mississippi Valley Medical Editors' Association**—No further meetings of the Mississippi Valley Medical Editors' Association will be held for the duration of the war

# ARCHIVES of INTERNAL MEDICINE

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## VASCULAR DISEASE FOLLOWING TOXEMIA OF PREGNANCY (PREECLAMPSIA AND ECLAMPSIA)

### OBSERVATIONS ON ITS CLINICAL COURSE

ABNER GOLDEN, M D

LEWIS DEXTER, M D

AND

SOMA WEISS, M D †

BOSTON

Most studies of persistent hypertension following toxemia of pregnancy have been of a statistical nature. We are not familiar with any work that describes in detail the clinical course. It is our purpose to do this in the hope that it will provide a better understanding of the nature and importance of this disease and stimulate others to amplify our observations. As we shall see, the clinical analogy of toxemia of pregnancy and its late effects to acute glomerulonephritis and its sequelae is striking despite a distinct difference in the etiologic and the pathologic aspects of the two diseases. It will, perhaps, be convenient to bear in mind this analogy in considering the material to be presented. It must be emphasized, however, that the two diseases are different etiologically and pathologically.

In this report we have confined our studies to cases in which toxemia of pregnancy was imposed on a previously normal cardiovascular renal system. Those cases in which toxemia aggravated preexisting hypertensive disease have not been included. We have encountered a sizable group of cases of hypertension in women in which it was suspected that the vascular disease originated in a toxemic pregnancy. For the purpose of this study, however, we have had to exclude many of these cases because of inadequate data. With 1 exception we have illustrated the important features of the course of post-toxemic hypertension by using only those cases in which the blood pressure and the urine were known to have been normal before or early in pregnancy, in which an accurate record of the toxemic course during pregnancy could be obtained and in which the blood pressure was determined and urinalysis was performed at frequent intervals post partum.

### DEFINITION OF TOXEMIA OF PREGNANCY

Elsewhere two of us (L. D. and S. W.)<sup>1</sup> have defined toxemia of pregnancy (preeclampsia and eclampsia) as an acute vascular disorder characterized by the appearance in the latter half of pregnancy of (a) an abnormal elevation of blood pressure above the prepregnancy level (regardless of the presence or absence of

† Deceased

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This investigation was made possible by a grant from the John and Mary R. Markle Foundation and from the Armour Laboratories

1. Dexter, L., and Weiss, S. Preeclamptic and Eclamptic Toxemia of Pregnancy, Boston, Little, Brown & Company, 1941



hypertensive disease before the onset of pregnancy) or (b) an increase in the degree of albuminuria above the prepregnancy level in the absence of other obvious cause and (c) generalized edema in association with the foregoing changes in the majority of instances and (d) a rapid diminution of these abnormalities before or soon after delivery. Symptoms may or may not be present.

#### CRITERIA FOR THE DIAGNOSIS OF TOXEMIA OF PREGNANCY

Criteria for the diagnosis of toxemia of pregnancy have been discussed elsewhere at length.<sup>2</sup> The presence of hypertension or albuminuria in pregnancy does not necessarily imply the existence of toxemia. Diagnosis depends on recording a significant increase during the last half of pregnancy in blood pressure or degree of albuminuria above the level present before pregnancy, or during the first half. Determination of the presence or absence of hypertensive disease in the pregnant, as well as in the nonpregnant, woman is almost impossible in borderline cases, despite the introduction of ingenious diagnostic measures in recent years. It is not rare for the blood pressure to fall, particularly during the second trimester of pregnancy,<sup>3</sup> as in animals with experimental renal hypertension.<sup>4</sup> Should previous hypertension be mild, normal values may be recorded. The following case is an example of this. Hypertension persisted after toxemia in the second preg-

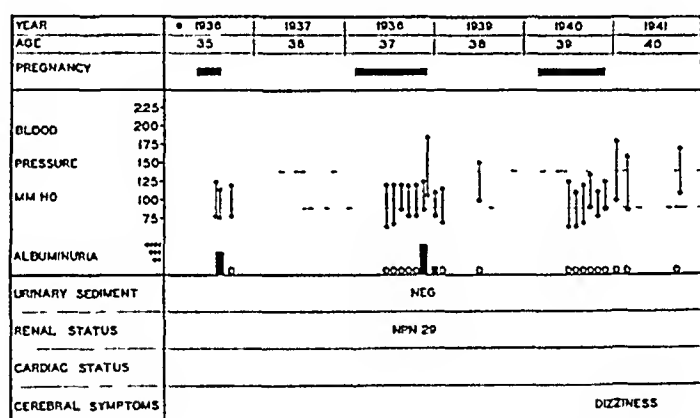


Fig 1 (case 1)—Post-toxemic hypertension

nancy. During the third pregnancy, two years later, the blood pressure was high, normal on many occasions, and one month post partum definite hypertension was again present. Although it is infrequent to encounter normotension in a hypertensive patient during pregnancy, this case is included to illustrate the difficulty that may occur in evaluating measurements of blood pressure during gestation.

**CASE 1 (fig 1)**—B. D., a Negress, had no history of vascular or renal disease in the past. Her first pregnancy, in 1936 when she was 35 years old, was terminated at three months by a spontaneous abortion, at which time the blood pressure was 126 systolic and 80 diastolic and urinalysis revealed albumin (3 plus). One week after delivery, the blood pressure was

2 Dexter, L., Weiss, S., Haynes, F. W., and Sise, H. S. Hypertensive Toxemia of Pregnancy. Preeclampsia and Eclampsia, *J. A. M. A.* **122**: 145 (May 15) 1943. Dexter and Weiss.<sup>1</sup>

3 (a) Reid, D. E., and Teel, H. M. Non-Convulsive Pregnancy Toxemias. Their Relationship to Chronic Vascular and Renal Disease, *Am. J. Obst. & Gynec.* **37**: 886 (May) 1939. (b) Dieckmann, W. J., and Brown, I. Hypertension and Pregnancy, *ibid.* **36**: 798 (Nov.) 1938. (c) Dexter and Weiss.<sup>1</sup>

4 Goldblatt, H., in discussion on Erickson, C. C., and Dill, L. V. Observations on the Effects of Renal Ischemia in Pregnant Dogs and Rabbits, *Am. J. Path.* **15**: 621 (Sept.) 1939. Dawson, J. R., Jr., Cressman, R. D., and Blalock, A. Experimental Hypertension and Pregnancy in Dogs, *ibid.* **17**: 31 (Jan.) 1941. Corbit, J. D., Jr. The Effect of Pregnancy upon Experimental Hypertension in the Rabbit, *Am. J. M. Sc.* **201**: 876 (June) 1941.

122 systolic and 80 diastolic and the urine was free of albumin. The prepartal record of the second pregnancy, in 1938, follows:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1938	4	122/66	0	0
	5	120/68	0	0
	6	118/88	0	0
	7	120/80	0	0
	8	120/80	0	0
	9	184/104	++++	0

Eighteen days before delivery, the blood pressure was 126 systolic and 88 diastolic and the urine contained albumin (4 plus). The urinary sediment was normal. The blood pressure rose, reaching 184 systolic and 104 diastolic before the onset of labor, and large amounts of albumin persisted in the urine. Delivery was spontaneous and the fetus viable. Post partum her course was as follows:

Year	Time Post Partum	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1939	7 days	110/80	+	0
	12 days	115/70	0	0
	1 mo	150/100	±	Headaches, dizziness
	6 mo	150/100	0	0
1940	1 yr	160/100	0	0
1941	2½ yr	160/90	0	Dizziness
1941	3 yr	170/110	0	0

A third pregnancy occurred in 1940, two years after toxemia. The prepartal record was as follows:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1940	4	126/64	0	0
	5	110/64	0	0
	6	122/70	0	0
	7	134/96	0	0
	8	110/80	0	0
	9	128/90	0	0

One month post partum, however, the blood pressure was 180 systolic and 100 diastolic and remained elevated for at least one year.

Occasionally, there is extreme difficulty in ruling out borderline hypertensive disease antedating pregnancy. This is illustrated by case 2. During the early months of pregnancy the blood pressure was consistently at the upper border of normal, although the patient was not definitely hypertensive at any time. Toxemia developed during the last trimester followed by definite persistent postpartum hypertension. It is possible that this patient had mild hypertension before pregnancy and that it became aggravated by toxemia.

CASE 2 (fig 2)—F. S. gave no history of vascular disease in the past. Her only pregnancy took place in 1933, when she was 30. The course during pregnancy is summarized below:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1933	3	134/86	0	Nausea, vomiting
	4	130/88	0	0
	5	125/76	0	0
	6	135/90	0	0
	7	160/105	0	0
	8	150/100	+	0
	9	164/110	+	0



The patient was admitted to the hospital when she was seven and a half months pregnant, and with conservative therapy the blood pressure fell to 150 systolic and 100 diastolic. When she was eight and a half months pregnant, however, she was readmitted with severe preeclampsia, delivery was normal, and the fetus died a few days after birth. Post partum her course was as follows:

Year	Time Post Partum	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1935	5 days	124/80	+++	0
1935	10 days	118/88	+++	0
1936	3 mo	140/94	+	0
1936	1 yr	160/110	±	Scotomas, enlarged heart
1938	3 yr	170/110	+	Scotomas, vertigo, nocturia with urination one to two times
1940	5 yr	164/110	++ . 0	

At the time of her last postpartum visit the patient had a convulsion lasting five minutes. Her husband revealed that she had had similar attacks every two to three months during the previous two years.

#### FACTORS INFLUENCING THE DEVELOPMENT OF PERMANENT POSTPARTUM VASCULAR DISEASE

It has been emphasized elsewhere<sup>2</sup> that by far the most important factor determining the persistence of postpartum hypertension is the duration of the hypertension or the albuminuria during pregnancy no matter how mild it is. Of decidedly secondary importance is the severity of the toxemia. Indeed, after eclampsia permanent vascular sequelae are uncommon.<sup>5</sup> We have advocated the termination of pregnancy after three weeks in cases in which toxemia does not respond to conservative therapy. Peckham<sup>6</sup> suggested termination of pregnancy after four weeks for this same reason. In the cases reported here it will be noted that the majority of women had preeclampsia, usually mild, and that it persisted for several weeks during pregnancy. Case 6 is exceptional in that permanent vascular damage followed eclamptic toxemia of short duration. Post-toxemic vascular disease is, therefore, one of the few types of hypertension which is often preventable.

#### EARLY STAGES OF POST-TOXEMIC HYPERTENSION

Although it is common for the blood pressure and the urine to return to normal within a few days or weeks after the termination of a toxemic pregnancy, hypertension and albuminuria in some instances may persist for months before disappearing. Such occurrences are not rare.

On the other hand, both blood pressure and urine may return to normal within a few days or weeks, and subsequently hypertension or albuminuria may reappear. How long this "latent" period may exist is a matter of conjecture and is extremely difficult to evaluate, as other causes may supervene to play a role in the production of subsequent vascular disease. We have seen instances in which hypertension did not reappear for as long as five years or more after toxemia of pregnancy,

5 Teel, H. M., and Reid, D. E. Eclampsia and Its Sequelae. A Clinical Follow-Up of All Cases at the Boston Lying-In Hospital over a Twenty Year Period, *Am J Obst & Gynec* **34** 12 (July) 1937.

6 Peckham, C. H., Jr. Time of Onset and Duration of the Toxemias of Late Pregnancy in Relation to the Development of Permanent Vascular Damage, *Am J Obst & Gynec* **42** 638 (Oct) 1941.

but it is obviously impossible to decide what influence pregnancy had on the development of the hypertension under such circumstances. In the following case toxemia of pregnancy was characterized predominantly by albuminuria. The urine was free of protein six months post partum, but it contained albumin (2 plus) two years later.

CASE 4 (fig 4)—II C had a past and a familial history which was noncontributory. Her only pregnancy, in 1938 and 1939 when she was 19 years old, can be summarized as follows:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1939	5	110/60	0	0
	6	120/60	0, ±	0
	7	120/60	0	0
	8	130/70	0	Slight edema
	9	132/82	++	Moderate edema

The urinary sediment was normal at all times. There was a 71 pound (32 Kg) gain in weight during pregnancy. Delivery, which was spontaneous and normal, was followed by a rapid

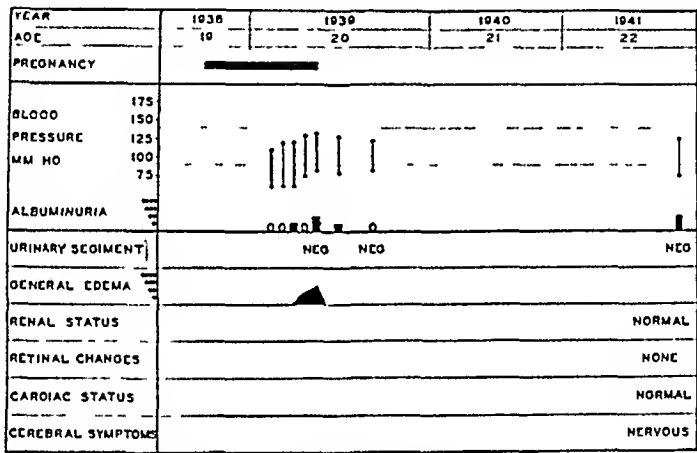


Fig 4 (case 4)—Post-toxemic albuminuria

diuresis. Two months post partum, the blood pressure was 128 systolic and 80 diastolic and the urine contained albumin (1 plus). The patient had lost 40 pounds (18 Kg) and had no complaints. Four months later the urine was free from protein. Two and one-half years after pregnancy, the blood pressure was 125 systolic and 75 diastolic but the urine contained albumin (2 plus). She was asymptomatic except for occasional edema of the ankles.

That a period of normalcy may exist between a toxemic pregnancy and the appearance of permanent recognizable vascular disease is unquestioned. Such factors as trauma of delivery, anesthesia and rest in bed undoubtedly mask the permanent vascular disease in some instances. The tendency of attributing hypertensive disease to a toxemic pregnancy that occurred many years before is common and often unjustifiable, since other causes of the hypertension may have arisen during the interim.

In the majority of cases of post-toxemic hypertension or albuminuria, blood pressure and urine never return to normal after delivery. The level of the blood pressure remains borderline or definitely elevated, and variable amounts of albumin persist in the urine. This early phase is illustrated in cases 5 to 8.

## COURSE OF POST-TOXEMIC HYPERTENSION

In those persons in whom permanent vascular disease develops after toxemia of pregnancy the course is one of chronic progression, as in other types of hypertensive disease. At first the blood pressure may be borderline, normal on one occasion and somewhat elevated on another. In other cases it is definitely elevated on all occasions. Over a period of years it may gradually increase to high levels, or both systolic and diastolic pressures may suddenly rise from a moderate to a high level and take on the clinical aspects of malignant hypertension, as in case 5. In other instances, the course may be malignant from the start, as in case 7. We have been impressed by the rapid progression of the course of post-toxemic hypertension, the high levels to which both systolic and diastolic blood pressures may rise and the malignancy of the terminal phases of the disease.

Albuminuria may be the only indication of permanent residual renal impairment following toxemia (cases 4 and 8). This may persist in small or large degree for years unaccompanied by hypertension. The urinary sediment may contain many hyaline and granular casts and erythrocytes, resembling in every respect the urine of patients with chronic glomerulonephritis. We have not observed any instances of the so-called "nephrotic stage" of chronic glomerulonephritis in any of our cases of post-toxemic hypertension and albuminuria. Rapidly progressive hypertension may appear terminally (case 8), often in conjunction with renal failure, as in other types of chronic renal disease with albuminuria, such as chronic pyelonephritis and chronic glomerulonephritis.

At other times both hypertension and albuminuria are present throughout the postpartum course (cases 3 and 7). It is our impression that in those cases in which toxemia has been characterized mainly by hypertension during pregnancy the course post partum is predominantly hypertensive and that in those in which the toxemia is characterized primarily by albuminuria the course post partum is predominantly albuminuric.

Once established the post-toxemic hypertensive vascular disease resembles closely that of other types of vascular hypertension. For years there may be no symptoms whatsoever. Eventually, however, the brain, heart or kidneys succumb to the ravages of the disease, as in hypertensive disease of other causation. Such cerebral symptoms as headache, dizziness, nervousness, irritability, insomnia and paresthesia and eventually aphasia and hemiplegia may develop. The heart, at first normal, becomes enlarged, and symptoms and signs of cardiac insufficiency may appear. Finally, frank failure may ensue. Renal function, as determined by the urea clearance test, the concentration test and the phenolsulfonphthalein test may gradually and progressively diminish over the course of years. With the advent of frank renal insufficiency there is nitrogen retention in the blood.

Recent studies of renal clearance<sup>7</sup> have indicated that during toxemia of pregnancy the renal blood flow is essentially normal and the filtration rate some-

7 Chesley, L. C., Connell, E. J., Chesley, E. R., Katz, J. D., and Glissen, C. S. The Diodrast Clearance and Renal Blood Flow in Toxemias of Pregnancy, *J. Clin. Investigation* **19** 219 (Jan.) 1940. Chesley, L. C. The Question of Glomerular Damage Following Toxemia of Pregnancy, *Am. J. Obst. & Gynec.* **42** 229 (Aug.) 1941. Corcoran, A. C., and Page, I. H. Renal Function in Late Toxemia of Pregnancy, *Am. J. M. Sc.* **201** 385 (March) 1941. Taylor, H. C., Jr., Wellen, I., and Welsh, C. A. Renal Function Studies in Normal Pregnancy and in Toxemia Based on Clearances of Inulin, Phenol Red, and Diodrast, *Am. J. Obst. & Gynec.* **43** 567 (April) 1942. Welsh, C. A., Wellen, I., and Taylor, H. C., Jr. Renal Blood Flow, Filtration Rate, and Tubular Excretory Mass in Patients with Specific Toxemia of Pregnancy, *J. Clin. Investigation* **20** 438 (July) 1941. Wellen, I., Welsh, C. A., and Taylor, H. C., Jr.

what decreased. In those cases in which permanent postpartum hypertension develops, however, the clearances change after delivery in a manner indicating a decreased renal blood flow and an increased filtration rate, as in other types of chronic hypertensive disease. These observations contribute to the evidence that post-toxic hypertension is similar to the chronic types of hypertensive disease, such as essential hypertension and chronic glomerulonephritis, and differs from the acute hypertension of toxemia.

In our experience, cases in which the course is primarily albuminuric are prone to terminate in renal insufficiency, whereas in those in which the course is predominantly hypertensive cardiac failure or cerebral hemorrhage develops terminally.

It is of value to follow a patient's course by periodic retinal examination. Vascular spasm, papilledema, retinal detachment, hemorrhages and exudates may appear during toxemia, but post partum they ordinarily disappear in the course

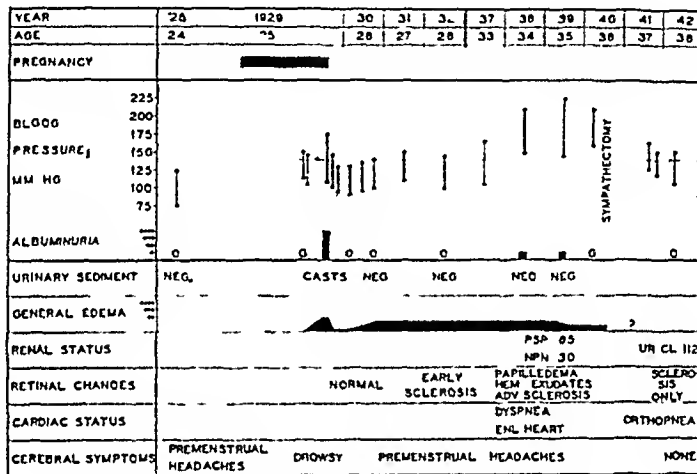


Fig 5 (case 5) —Post-toxic hypertension

of weeks or months as the hypertension and albuminuria diminish.<sup>1</sup> During the ensuing years of post-toxic hypertension the retinal vessels gradually become narrowed and their lumens irregular. The light reflex is increased, and arterio-venous "compression" becomes pronounced. The appearance of retinal hemorrhages and various types of exudate is usually an ominous sign. To date, we have not seen the classic albuminuric retinitis in the eyegrounds of any of our patients.

The following cases illustrate the salient features of post-toxic hypertension.

CASE 5 (fig 5) —C H had had uncomplicated scarlet fever at the age of 2. Otherwise, the past history was noncontributory. Being a nurse, she was known to have had normal blood pressure (120 systolic and 75 diastolic) and urine before and after her marriage, in 1928. She became pregnant in 1929, at the age of 25. Blood pressures and results of urinalysis were normal through the twentieth week. At this time, the blood pressure rose to 148 systolic and 112 diastolic without albuminuria and she complained of morning headaches. Despite therapy the blood pressure remained elevated for the next nine weeks. During the twenty-ninth week she was found to have a blood pressure of 170 systolic and 106 diastolic and albumin (4 plus) in the urine, together with moderate generalized edema. After ten days of conservative therapy, the blood pressure remained the same, she became drowsy and labor was induced. A nonviable fetus was delivered. Post partum her blood pressure fell to 130 to 140 systolic and 90 to 100 diastolic for six months. Albuminuria disappeared, but she complained of intermittent edema.

The Filtration Rate, Effective Renal Blood Flow, Tubular Excretory Mass and Phenol Red Clearance in Specific Toxemia of Pregnancy, *ibid* 21 63 (Jan) 1942. Dill, L. V., Isenhour, M. A., Cadden, M. A., and Schaffer, N. K. Glomerular Filtration and Renal Blood Flow in the Toxemias of Pregnancy, *Am J Obst & Gynec* 43 32 (Jan) 1942.

From 1930 to 1937 the blood pressure remained at about 140 systolic and 110 diastolic with intermittent edema and no albuminuria. In 1937 the blood pressure rose rapidly to 175 to 240 systolic and 136 to 160 diastolic. The heart was found to be somewhat enlarged, and there was exertional dyspnea. Retinal hemorrhages and exudates and advanced changes in the vessels of the eyes appeared. The urine contained albumin (1 plus), but renal function as judged by the usual tests was normal. In 1941 sudden blindness associated with clouding of the sensorium occurred transiently. The patient complained of constant severe headache. A thoracolumbar sympathectomy was performed shortly thereafter by Dr Reginald H. Smithwick, after which the blood pressure fell to about 155 systolic and 110 diastolic, the eyegrounds



Fig 6 (case 5)—Biopsy section of renal tissue. Note the glomerular destruction, the arteriolar thickening and the relatively normal tubules. Phloxine-methylene blue stain,  $\times 320$ .

improved, symptoms disappeared except for those associated with postural hypotension and renal function remained normal.

A biopsy of renal tissue (fig 6) at the time of sympathectomy revealed advanced nephrosclerosis. The majority of the glomeruli were damaged, many being destroyed or hyalinized. Most of the tubules, on the other hand, appeared relatively normal in the biopsy section, although some showed minor degrees of atrophy. There was little increase in connective tissue elements. The arteriolar changes were striking and were characterized by muscular thickening of the media and narrowing of the lumens. These changes are those of nephrosclerosis.



*Comment*—Normal prior to pregnancy, this patient experienced severe pre-eclampsia which lasted for ten weeks. Hypertension persisted post partum and became clinically malignant eight years after pregnancy, although it has been relieved at least temporarily by extensive sympathectomy.

CASE 6 (fig 7)—B. N., a Negress, had a noncontributory familial and past history. There are no data available on her first four pregnancies. The fifth through the eighth pregnancy can be summarized as follows:

Pregnancy No	Year	Highest Blood Pressure, Systolic/Diastolic	Albumin in Urine
5	1922	110/70	0
6	1925	Miscarriage	
7	1929	120/70	Rare +
8	1930	120/80	0

The ninth pregnancy occurred in 1932, when the patient was 38 years old, and was normal until the sixth month, when the blood pressure was 125 systolic and 80 diastolic and the urine did not contain albumin. Less than two weeks later she was admitted to the hospital because of three convulsions the day of entry. Her blood pressure was 222 systolic and 120 diastolic and the urine contained albumin (1 to 2 plus). After the administration of magnesium sulfate

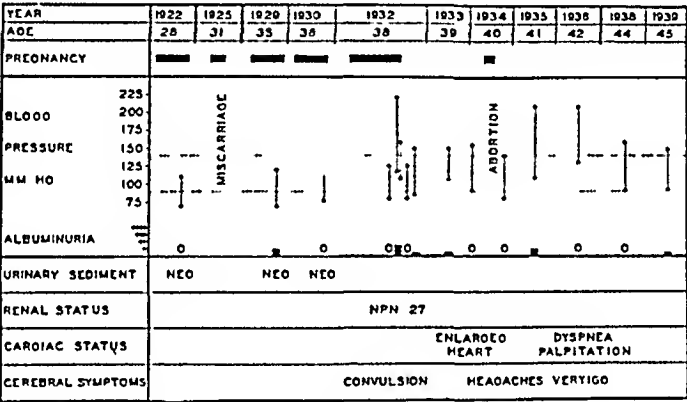


Fig 7 (case 6) —Post-toxemic hypertension

the blood pressure fell to 160 systolic and 110 diastolic. Five days later she was delivered spontaneously of a macerated fetus. Her postpartum course has been summarized as follows:

Year	Time Post Partum	Blood Pressure Systolic/Diastolic	Albumin In Urine	Symptoms
1932	7 days	150/100	+	0
	12 days	126/80	0	0
	1 mo	150/86	±	Headaches
1933	1 yr	150/106	±	Headaches, enlarged heart
1933	1½ yr	156/90	0	Headaches, enlarged heart
1934	(Abortion and sterilization when patient 2½ months pregnant)			
1934	2 yr	140/80	0	Headaches
1935	3 yr	210/110	+	Headaches, vertigo, dyspnea, edema of the legs, palpitation
1936	4 yr	210/130	0	Palpitation
1938	6 yr	160/90	0	Headaches, dyspnea, vertigo
1939	7 yr	150/90	±	Headaches, dyspnea, vertigo

*Comment*—This is a rare example of permanent hypertension following an eclamptic pregnancy. The blood pressure and the urine had been normal during several earlier pregnancies. Convulsions occurred suddenly during the sixth month of the ninth pregnancy accompanied by severe hypertension and minimal edema. For at least seven years following eclampsia the patient had hypertension with cardiac and cerebral symptomatology but with albuminuria rarely.

CASE 7 (fig 8)—M. L. O. had a noncontributory familial and past history. The first pregnancy occurred in 1935, when she was 18. There is no record of determination of blood pressure or examination of urine before or during the early months of pregnancy. She was admitted to the hospital during the eighth month with a blood pressure of 180 systolic and 140 diastolic and albumin (4 plus) in the urine. The sediment contained many white cells and an occasional cast. A stillborn infant was delivered shortly thereafter. After delivery the blood pressure remained elevated and albuminuria persisted, although she was symptom free.

In 1938 she delivered another stillborn infant. Shortly before delivery, the blood pressure was 224 systolic and 150 diastolic, and the urine contained albumin (4 plus). The sediment showed an occasional white blood cell and no casts. She was complaining of vomiting and blurring of vision. Examination revealed a detached retina. A third pregnancy terminated in a spontaneous abortion at three months. Vomiting had been the only symptom.

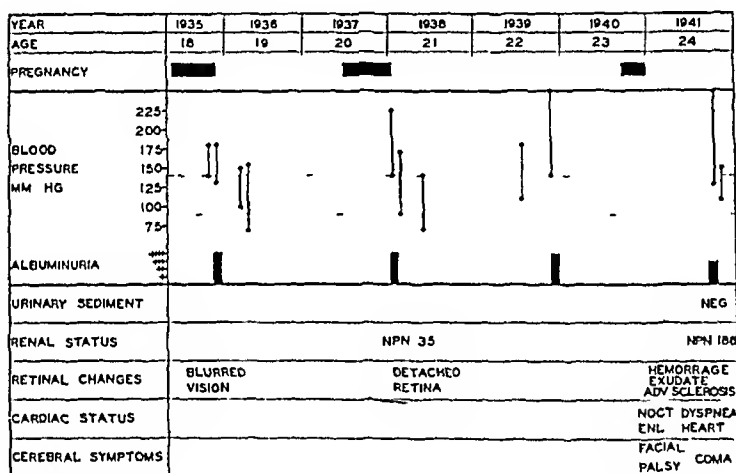


Fig 8 (case 7)—Post-toxemic hypertension and albuminuria

In 1941 she suffered a palsy of the left side of the face which persisted. Severe headaches and vomiting appeared. She was admitted to the hospital in severe cardiac decompensation. The blood pressure was 250 systolic and 130 diastolic, the urine contained albumin (3 plus), and the urinary sediment contained 10 to 15 red cells, occasional white cells and no casts. The blood level of nonprotein nitrogen was 186 mg per hundred cubic centimeters. The patient died in uremia shortly thereafter.

At autopsy, the kidneys were small and contracted and the surface was granular. The capsule was thickened and adherent. The cortex was irregular and considerably thinner than normal. There was no evidence of pyelonephritis. Microscopically, the renal changes were those primarily of nephrosclerosis. The walls of the renal arterioles were greatly thickened, and narrowing of their lumens was pronounced, as may be seen in figure 9. Some glomeruli were intact, others obliterated and still others in various stages of destruction. Marked atrophy and destruction of tubular tissue were present with relatively few functioning units still intact. The destruction of glomeruli and tubules was reflected by a pronounced relative increase in the interstitial connective tissue.

The liver grossly and microscopically showed no abnormalities.

*Comment*—The clinical history suggests that vascular disease was caused by toxemia of both the first and the second pregnancy. The course following the

second pregnancy was one of malignant vascular disease with death due to cardiac and renal insufficiency. Unfortunately, there is no record of blood pressure and urinalysis before the first pregnancy. Since autopsy showed nephrosclerosis and failed to reveal other causes for the vascular disease, it seems plausible to assume that it was caused by the toxemia of both the first and the second pregnancy.



Fig 9 (case 7) —Section of kidney, showing advanced arteriolar thickening, glomerular and tubular destruction and interstitial fibrosis. Eosin-methylene blue stain,  $\times 160$ .

CASE 8 (fig 10) —A. E. G. had a familial and past history which was of no significance. In 1922 results of a urinalysis were normal. During her first pregnancy, at the age of 25 in 1928, there were nausea and vomiting and generalized edema during the last trimester. At term, the blood pressure was 140 systolic and 86 diastolic and albumin (2 plus) was present in the urine, together with a few red cells and many hyaline and granular casts. In the latter half of the second pregnancy, in 1929, the blood pressure varied between 100 to 120 systolic and 70 to 80 diastolic throughout and the urine showed albumin (4 plus) on all occasions. There were

no toxemic symptoms. Labor was induced two weeks before term, and a normal infant was delivered. In 1932, between pregnancies, albumin (2 plus) was noted in the urine. In the same year there was an abortion at the third month of pregnancy, at which time the blood pressure was 120 systolic and 80 diastolic and the urine contained albumin (2 plus). During the fourth pregnancy, in 1935, albumin (4 plus) with occasional red cells and casts was noted in the urine at the eighth month and the blood pressure was 110 systolic and 80 diastolic. Delivery of a normal child occurred. From 1935 to 1940 the patient felt well and active. In 1940 fatigue, headaches, vomiting and blurred vision appeared. The blood pressure was found to be 215 systolic and 135 diastolic, the urine contained albumin (2 to 3 plus) and many red cells and casts, retinal vascular changes and hemorrhages were present, and frank cardiac failure and renal insufficiency (blood level of nonprotein nitrogen, 123 mg per hundred cubic centimeters) were manifest. She went rapidly downhill and died of cardiac failure and uremia.

At autopsy both kidneys were contracted and presented a granular surface. The capsule was thickened, although not adherent. Several small cysts were present in the cortex of the left kidney. Microscopically, the renal architecture was markedly distorted, showing extensive areas of scarring and some areas of tubular hypertrophy and dilatation (fig 11). All of the glomeruli were damaged, many being completely sclerosed and hyalinized. Many of the tubules were atrophic, while others showed evidence of regeneration. There was a diffuse increase in connective tissue elements. The arteriolar changes were striking. There was concentric

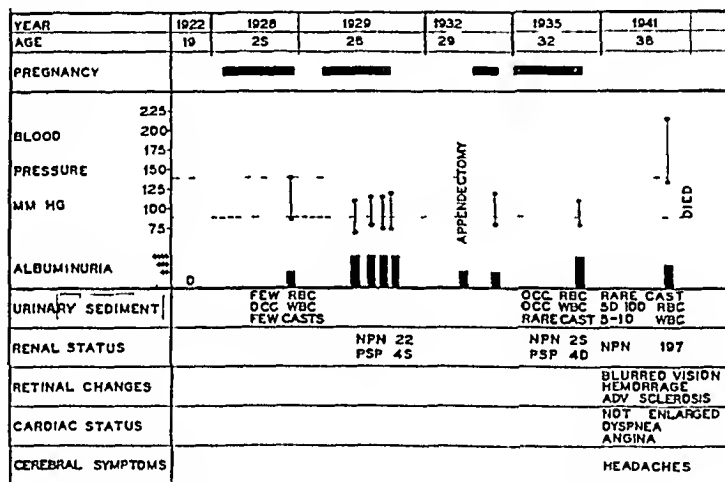


Fig 10 (case 8) —Post-toxemic albuminuria

thickening of the media with encroachment of the lumens. The larger vessels showed irregular hyaline intimal thickening and some medial fibrosis. No necrotizing lesions were seen.

No evidence of cirrhosis was found on histologic examination of the liver. Changes consistent with chronic passive congestion were the only abnormalities.

*Comment*—After an albuminuric pregnancy in 1928 this patient's condition, previously normal, ran a course characterized mainly by albuminuria and terminal hypertension, with death due to uremia and cardiac failure.

The following case of post-toxemic hypertension is presented despite a lack of precise clinical data. In this case too, renal tissue for biopsy was taken at the time of sympathectomy.

**CASE 9**—E M, aged 35, had nothing of significance in the familial and past history. Since the menarche she had had severe left-sided headaches with scintillating scotomas, nausea and vomiting premenstrually. The headaches became less severe and less frequent after marriage in 1929. During her first pregnancy, in 1931 at the age of 25, she had visited her physician monthly, starting at the second month. Blood pressure and urine were said to have been normal until the eighth month. During the seventh month massive edema of hands, feet and face appeared. One month before delivery hypertension and albuminuria were said to have appeared for the first time. She was treated medically and was delivered of a normal infant at term. The blood pressure remained elevated after this pregnancy, and small amounts of albumin were noted

in the urine on many occasions. Pregnancies occurred in 1933, 1935 and 1937. Two further pregnancies, in 1938 and 1940, were interrupted because of progressing hypertension. In 1942, the blood pressure was 230 systolic and 140 diastolic and the urine contained albumin (1 plus). The patient had complained of intense weakness for the two preceding years. She appeared worn and prematurely gray. Retinal examination showed only mild vascular change without



Fig 11 (case 8) —Section of kidney, showing extensive scarring, damaged glomeruli and pronounced arteriolar changes. Eosin-methylene blue stain,  $\times 160$

hemorrhage or exudate. Renal function was normal. In May 1942, the blood pressure was 275 systolic and 140 diastolic and the urine contained variable amounts of albumin (on one occasion the reaction for albumin was as great as 3 plus). A sympathectomy was performed in May 1942 by Dr. Reginald H. Smithwick, and renal tissue for biopsy was taken at the time of operation.

*Renal Biopsy* (fig 12) —The renal arterioles showed sclerotic changes which, however, were not severe. The outstanding renal lesion microscopically was a diffuse degeneration of the tubular epithelium with swelling, degeneration, loss of contour and destruction. The glomeruli were only slightly damaged. Interstitial tissue was not increased.

## COMMENT

Toxemia of pregnancy (preeclampsia and eclampsia) occurs in approximately 6 to 9 per cent of all pregnancies.<sup>8</sup> Furthermore, from examination of published reports it is apparent that roughly 25 per cent of women in whom toxemia develops are left with permanent postpartum vascular disease.<sup>9</sup> While these figures may be



Fig 12 (case 9) —Biopsy section of renal tissue, showing diffuse degeneration of the tubular epithelium. Phloxine-methylene blue stain,  $\times 320$ .

8 Stander, H. J. An Analysis of Eight Hundred and One Cases of Toxemias of Pregnancy, *New England J Med* **201** 458 (Sept 5) 1929. Dieckmann, W. J. Renal Function in the Toxemias of Pregnancy, *Am J Obst & Gynec* **29** 472 (April) 1935. Page, E. W. Relation Between Hydatid Moles, Relative Ischemia of the Gravid Uterus, and the Placental Origin of Eclampsia, *ibid* **37** 291 (Feb) 1939.

9 (a) Herrick, W. W., and Tillman, A. J. B. Toxemia of Pregnancy: Its Relation to Cardiovascular and Renal Diseases, Clinical and Necropsy Observations with a Long Follow-Up, *Arch Int Med* **55** 643 (April) 1935. (b) Dieckmann, W. J., and Brown, I. Do Eclampsia and Pre-Eclampsia Cause Permanent Vascular Renal Pathology? *Am J Obst & Gynec* **37** 762 (May) 1939. (c) Reid and Teel.<sup>3a</sup> (d) Teel and Reid.<sup>5</sup>

high because of existing difficulties in the classification of cases derived from various sources, it will be noted, if one assumes their validity, that in 2 per cent of all women who become pregnant permanent hypertension develops after pregnancy

The question has been raised as to whether toxemia has brought to light hitherto latent and unrecognized hypertension or whether it has actually been the factor initiating the vicious circle of permanent hypertensive disease. We believe the latter to be true in the light of the known facts both of clinical and of experimental hypertension

Toxemia of pregnancy is a well defined disease entity. It is an acute type of vascular disease occurring during the last half of pregnancy, usually accompanied by greater or lesser degrees of water retention, sometimes subsiding before delivery and always after delivery. It may appear in women with hitherto normal blood pressure as well as in those who are already hypertensive.

Its closest analog in a nonpregnant person is acute glomerulonephritis, from which it differs clinically mainly by the absence of preceding infection of the respiratory tract and lack of erythrocytes in the urinary sediment in all but the most severe cases. Just as acute glomerulonephritis differs clinically and pathogenetically from the chronic type of hypertension following it or from the hypertension appearing in association with pyelonephritis, endocrinopathies, arteritides, congenital anomalies or from the idiopathic type ("essential" hypertension), so does the vascular disorder of toxemia of pregnancy differ. There is no evidence warranting the postulation of previous latent hypertension in patients in whom acute glomerulonephritis and subsequent hypertension develop. Similarly, there is no good evidence for its existence in those in whom permanent hypertension develops after toxemia. Both diseases represent acute hypertension of short duration which may subside rapidly leaving no after-effects, may leave sequelae taking months to heal or may leave a permanent vascular disease which is to be clearly distinguished from the acute process which produced it and which in the meantime has subsided.

Isenhour and his co-workers<sup>10</sup> have recently studied average blood pressure and incidence of hypertension in a group of 900 parous and 900 nulliparous women subdivided into 10 year age groups. They found no increase in either the average blood pressure or the incidence of hypertension among the parous women, regardless of age group. The authors concluded that toxemia of pregnancy is not an etiologic factor in hypertension nor does it hasten its appearance in women predisposed to this disease. This conclusion does not seem warranted on the basis of a series which when subdivided into decades is so small. This is particularly evident in the younger age groups (20 to 29 and 30 to 39), in which the gross incidence of hypertension was comparatively low (about 2 and 5 per cent). If toxemia of pregnancy were responsible for 10 per cent of the instances of hypertension in these age groups, a much larger series than that reported would be required to show a significant increased incidence of hypertension due to this cause.

It is perhaps important to emphasize the obvious fact that chronic hypertensive disease is in itself a disease entity which after a certain stage is irreversible, even if the initiating lesion is removed, be it a unilateral pyelonephritic kidney or toxemia of pregnancy. The chronic forms of hypertensive vascular disease all behave similarly, as is indicated by the universal difficulty of differentiating the various causations on clinical and even on pathologic grounds. The brain, the heart and the kidneys are the organs most affected, and their eventual failure is the cause of death in the great majority of cases. The course of the chronic disease is flavored

<sup>10</sup> Isenhour, C. E., Kuder, K., and Dill, L. V. The Effect of Parity on the Average Blood Pressure and on the Incidence of Hypertension, *Am J M Sc* **203** 333 (March) 1942



somewhat by the initiating lesion. Thus in cases of so-called "essential" hypertension death occurs usually as a result of cerebral hemorrhage or cardiac failure. In cases of chronic glomerulonephritis, on the other hand, the majority of deaths are due to renal insufficiency. The course of post-toxemic hypertension may simulate that of chronic glomerulonephritis or that of benign or malignant "essential" hypertension. Death may result from cerebral hemorrhage, cardiac failure or uremia, particularly the last.

Heynemann<sup>11</sup> studied pathologically the kidneys of 7 patients dying years after eclamptic pregnancies and observed nephrosclerosis in 6 and chronic pyelonephritis in 1. Herrick and Tillman<sup>12</sup> described 11 cases of toxemia of pregnancy in which autopsy was done, on histologic examination they encountered nephrosclerosis in 7 cases and chronic glomerulonephritis in 4 cases. Bell<sup>13</sup> stated that he considered the pathologic change in toxemia to be a special form of glomerulonephritis, at least partially inflammatory in nature, and expressed the opinion that he could recognize characteristic lesions in the kidneys of a patient dying seven years after eclampsia. This work has not been confirmed, however, and Page and Cox<sup>14</sup> failed to find any specific pathologic condition post partum. The only constant change was a nonspecific thickening of the basement membrane of the glomerular capillaries. Thus, the observations of these various authors indicate that the kidneys of patients dying of hypertensive vascular disease which originated years earlier in a toxemic pregnancy have the histologic changes characteristic of chronic vascular nephritis (nephrosclerosis) or of chronic glomerulonephritis but not of preeclampsia or eclampsia. From our own data we are in accord with these observations and interpretations.

Histologic examination of the kidneys of our patients revealed nephrosclerosis as the basic and characteristic lesion. The characteristic renal changes of toxemia, the glomerulonephrosis of Fahr,<sup>14</sup> were absent. This indicates that the specific lesions of toxemia had "healed."

It is apparent that the kidneys may show a varied pathologic picture years after toxemia of pregnancy. Arteriolai change, consistent with hypertensive vascular disease, was seen in all our cases and in those reported by other investigators. The pathologic change may be limited to this lesion or may include varying degrees of glomerular scarring and tubular degeneration. It is frequently impossible to distinguish post-toxemic kidneys from those of chronic glomerulonephritis. This is not surprising, for the acute stages of both diseases are characterized by a diffuse glomerular lesion, inflammatory in the case of glomerulonephritis, degenerative in the case of toxemia. Just as the lesions of acute glomerulonephritis are not to be found in the kidneys of patients dying years later of chronic glomerulonephritis, so also glomerulonephrosis of Fahr,<sup>14</sup> characteristic of toxemia, is not encountered in the kidneys of persons dying years later of chronic vascular disease. This pathologic relation is of more than casual interest in view of the frequent similarity of both the acute and the chronic clinical syndrome. It is a common observation that the chronic effects of various types of initial renal lesions are identical or at least similar. In our cases, as well as in those reported by other investigators,

11 Heynemann, T. Spätfolgen der Eklampsie und ihrer Vorstadien unter besonderer Berücksichtigung der Nierenveränderungen, *Zentralbl f Gynak* 58 3010 (Dec 22) 1934.

12 Bell, E. T. Renal Lesions in the Toxemias of Pregnancy, *Am J Path* 8 1 (Jan) 1932.

13 Page, E. W., and Cox, A. J. Renal Changes Following Toxemias of Late Pregnancy, *West J Surg* 46 463 (Sept) 1938.

14 Fahr, T. Die pathologisch-anatomischen Veränderungen der Niere und Leber bei der Eklampsie, in Hinselmann, H. Die Eklampsie, Bonn, Friedrich Cohen, 1924.



the kidneys revealed changes practically identical with those in kidneys of patients dying of chronic glomerulonephritis and of "essential" hypertension

No evidence of cirrhosis of the liver was observed in our 2 cases in which autopsy was done

The importance of recognizing this group of patients with post-toxemic hypertension lies not so much in its treatment as in its prevention. In the great majority of cases this disease is preventable by interrupting pregnancy before the hypertension or albuminuria of toxemia has lasted for more than three weeks. This applies as much to mild as to severe toxemia. Furthermore, Irving<sup>15</sup> has demonstrated that the fetus, if anything, benefits by delivery occurring between the thirty-second and the thirty-sixth week of pregnancy rather than later. This is the commonest time of appearance of toxemia of pregnancy.<sup>1</sup>

#### SUMMARY

The rather common occurrence of permanent vascular disease following toxemia of pregnancy (preeclampsia and to a less extent eclampsia) is described and the clinical course of this hypertension studied.

The clinical analogy between toxemia of pregnancy and acute glomerulonephritis as regards the acute phases and the late effects on the vascular system is pointed out.

The duration, more than the severity, of the toxemia during pregnancy determines the development of permanent postpartum vascular disease.

A latent period of at least several months may intervene between toxemia of pregnancy and the development of recognizable permanent hypertension or albuminuria.

After toxemia of pregnancy hypertension may persist for at least a year and then disappear.

The postpartum course may be predominantly hypertensive or albuminuric, apparently dependent on a similar predominance in pregnancy.

The course is prone to be rapidly progressive in comparison with that of other types of hypertension.

Death usually occurs as a result of uremia, cardiac failure or cerebral hemorrhage, as in other types of hypertension. Retinal changes, such as vascular sclerosis, hemorrhages and exudates, occur, but no instances of true albuminuric retinitis have been observed.

Nephrosclerosis is the characteristic postmortem finding. The pathologic condition in the kidneys in other respects is variable, however, and at times may duplicate that of chronic glomerulonephritis. This is not surprising, as both diseases start with a diffuse glomerular lesion and the hypertensive vascular disorders following the two diseases may run almost identical clinical courses.

The importance of recognizing this group of patients with post-toxemic hypertension lies in its prevention. The late vascular effects of toxemia may be prevented by interrupting pregnancy before the hypertension and albuminuria of toxemia have lasted for more than three weeks. This applies as much to mild as to severe toxemia.

Dr. A. J. B. Tillman gave us permission to cite several cases from the records of the Sloane Hospital for Women, and Dr. Reginald H. Smithwick and Dr. Benjamin Castleman allowed us to examine the clinical and pathologic material in the 2 cases in which biopsy of renal tissue was done. Dr. Orville Bailey aided us in the interpretation of the pathologic material and photographed the microscopic sections presented.

Peter Bent Brigham Hospital

<sup>15</sup> Irving, F. C. A Study of Consecutive Cases of Hypertension and Albuminuria in Pregnancy, *Pennsylvania M. J.* **44**: 557 (Feb.) 1941.

# FRIEDLANDER'S BACILLUS SEPTICEMIA AND MENINGITIS

## REPORT OF A CASE AND AUTOPSY, WITH AN ANALYSIS OF TWENTY-NINE CASES COLLECTED FROM THE LITERATURE

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Meningitis caused by Friedlander's bacillus is a medical rarity. The case to be reported is of interest because of the scarcity with which reports of this disease have appeared in the American literature. It serves also to illustrate the danger of confusion with meningococcic meningitis. Until recently Friedlander's bacillus meningitis was almost uniformly fatal, but in the last two years some cures have been obtained with sulfapyridine<sup>1</sup> (2-[paraaminobenzenesulfonamido]-pyridine) as well as with sulfadiazine<sup>2</sup> (2-[paraaminobenzenesulfonamido]-pyrimidine), which has become available subsequent to the occurrence of our case. It is hoped that in the future early diagnosis and vigorous use of the proper drug may make successful treatment more generally possible. Since it appears that the dawn of a new era in the therapy of this formidable disease is being witnessed, a consideration of 29 cases collected from the available literature is included as a background against which present developments may be evaluated.

### REPORT OF CASE

*History*—E B J, a 73 year old white man, was brought to the hospital on Oct 30, 1940 in stupor. After a two year history of urinary symptoms culminating in complete retention he had entered another hospital six weeks previously. Treated with retention catheter, he improved and was discharged on October 24. At home he had no significant complaints until October 29, when he began to suffer from progressive headache, backache and malaise, followed by a shaking chill and fever, with a temperature of 103 F. On October 30 he became gradually less responsive and was admitted to the surgical service of Vanderbilt University Hospital.

*Physical Examination*—His temperature was 102 F (rectal), pulse rate 104, respiratory rate 24 and blood pressure 110 systolic and 70 diastolic. The patient was acutely ill and semiconscious. The pupils reacted normally, and there was no papilledema. The nose and ears were not remarkable. Moderate injection of the pharynx was observed. Most of the teeth were absent, and the remainder were extremely carious. Some increased resistance to flexion of the neck was noted, but true rigidity was not observed. Kernig's sign was absent. The heart did not seem enlarged on percussion, the rhythm was regular and no murmurs were heard. A few rales were detected at the bases of the lungs. The abdomen presented slight resistance without true muscle spasm. There was some tenderness in the right flank and costovertebral angle. The prostate was enlarged, irregular and firm. Several hard

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1 (a) Robertson, C W. Meningitis Due to B. Friedlanderi. Recovery of a Case Treated with Sulfapyridine, *Canad M A J* 45:70 (July) 1941. (b) Montes, G G, and Real, W A. Meningitis purulenta a neumobacilo de Friedlander (*Klebsiella pneumoniae*) curado con daganan, *Bol Soc cubana de pediat* 12:5 (Jan) 1940.

2 (a) Julianelle, L A. Personal communication to the authors. (b) Trevett, G I, Nelson, R A, and Long, P H. The Clinical Use of Sulfadiazine in the Therapy of Bacterial Infections Other than Pneumonia, *Bull Johns Hopkins Hosp* 69:303 (Oct) 1941.

nodules were noted in it and in the right seminal vesicle. The tendon reflexes were physiologic, the plantar response was flexor on both sides and clonus was absent.

*Course in Hospital*—The blood on admission contained 5,600,000 red cells and 22,000 leukocytes per cubic millimeter, 86 per cent of the latter being polymorphonuclear leukocytes, 10 per cent lymphocytes and 4 per cent monocytes. The hemoglobin measured 14 Gm per hundred cubic centimeters. The Kahn reaction of the blood was negative. Catheterization yielded 200 cc of cloudy urine containing 200 to 300 leukocytes and 3 or 4 erythrocytes per high power field in the centrifuged sediment. A trace of albumin was present, but there was no reduction with Benedict's solution. A retention catheter was inserted, and later specimens of urine revealed diminishing numbers of pus cells. The nonprotein nitrogen content of the blood was 50 mg per hundred cubic centimeters on admission but rose to 57 mg on the second hospital day despite the parenteral administration of fluids. On October 31 the patient sank into a coma, his neck became stiff and a lumbar puncture was done. The spinal fluid was purulent, was under an initial pressure of 150 mm and contained 2,800 cells, almost all of which were polymorphonuclear leukocytes. The reaction to Pandy's test was positive, and a pellicle formed when the fluid stood. No organisms were found in smears.

The patient was then transferred to the medical service. Examination revealed coma and rapid respirations with irregularly recurring intervals of apnea. The skin was sprinkled with petechiae varying from bright rose to dusky brown and from 1 to 3 mm in diameter, being most numerous on the chest but occurring also on the abdomen and extremities and in the palpebral conjunctiva of each eye. The neck was very stiff and Kernig's sign absent. A sustained ankle clonus and a questionable extensor plantar response were present on the left.

A hard shaking chill occurred. On the supposition that the patient was suffering from meningococcal meningitis, 6 Gm of sulfanilamide was administered by hypodermoclysis, and a Levine tube was inserted into the stomach, through which an additional 5 Gm was given, followed by 21 Gm every four hours with equal amounts of sodium bicarbonate. Lumbar puncture was repeated on the morning of November 1, with removal of 30 cc of turbid fluid containing 5,510 cells per cubic millimeter, of which 96 per cent were polymorphonuclear leukocytes. No definite organisms were found in Gram stains of the sediment after centrifugation. The level of free sulfanilamide in the blood and spinal fluid at that time were 20.2 and 15.1 mg per hundred cubic centimeters, respectively. The dose of the drug was reduced to 12 Gm and later in the day to 0.9 Gm, with equal amounts of sodium bicarbonate, given every four hours by Levine tube, and administration was continued at the latter dosage until the patient's death.

Toward evening lumbar puncture was repeated, with similar results. No organisms could be seen on careful search and cultures had not as yet shown growth. This strengthened the impression of meningococcal infection, and the patient was given intravenously 60,000 units of meningococcus antitoxin (Parke, Davis & Company) diluted with 10 per cent dextrose solution. Later the pulse became very rapid and an electrocardiogram showed auricular flutter. Fever persisted, the temperature reaching as high as 105.4 F (fig 1). Death occurred on the morning of November 2, early in the fifth day of illness and about sixty-eight hours after admission to the hospital.

*Bacteriologic Observations*—Spinal fluid obtained on October 31 yielded no growth on blood agar, on cooked chocolate agar slants or in dextrose infusion and sodium thioglycollate broths. Two specimens of spinal fluid taken on November 1 showed Friedlander's bacillus in all these mediums. Cultures of urine taken on October 31 and November 1 showed pure growth of the same organism, which was also shown by the patient's blood drawn October 31 before institution of sulfanilamide therapy but only in dextrose broth after thirty-six hours' incubation.

Study of the organism showed it to be a nonmotile, pleomorphic, gram-negative encapsulated bacillus with rounded ends and a tendency to bipolar staining. On blood agar the colonies were round, white, lustrous, opaque, mucoid and characteristically stringy when touched with the loop. Growth was luxuriant and confluent in subcultures on solid mediums, including plain beef infusion agar. There was no hemolysis of blood agar or blood broth. Abundant growth occurred in sodium thioglycollate broth,<sup>3</sup> demonstrating facultative anaerobiosis. Lactose, dextrose, xylose, mannitol, maltose and sucrose were readily fermented, with production of acid and gas. Tests for indole formation gave negative results. A white mouse

<sup>3</sup> Brewer, J. H. Clear Liquid Mediums for the "Aerobic" Cultivation of Anaerobes, J. A. M. A. 115:598 (Aug 24) 1940.

was inoculated intraperitoneally with 0.25 cc of a twenty-four hour broth culture and died in less than eighteen hours. The same organism was recovered in large numbers from its heart's blood and stringy peritoneal exudate. Neither a *Quellung* reaction nor agglutination could be demonstrated in antipneumococcus type II serum. A subculture from the patient's spinal fluid was sent to Dr. Louis A. Julianelle, and he confirmed the identification of the organism as Friedlander's bacillus and classified it as serologic type B.

*Autopsy*—The body was somewhat emaciated. Petechiae were present over the body generally and in the conjunctival sacs. Moderate amounts of clear serous fluid were present in the peritoneal and pleural cavities. The pericardial sac was normal. The heart weighed 450 Gm, and a few small white opaque areas measuring 1 to 2 mm in diameter were present in the epicardium. Section revealed the same kind of lesions scattered throughout a thickened myocardium. The lungs showed only emphysema, but the bronchial mucosa con-

### FRIEDLAENDER'S BACILLUS SEPTICEMIA AND MENINGITIS

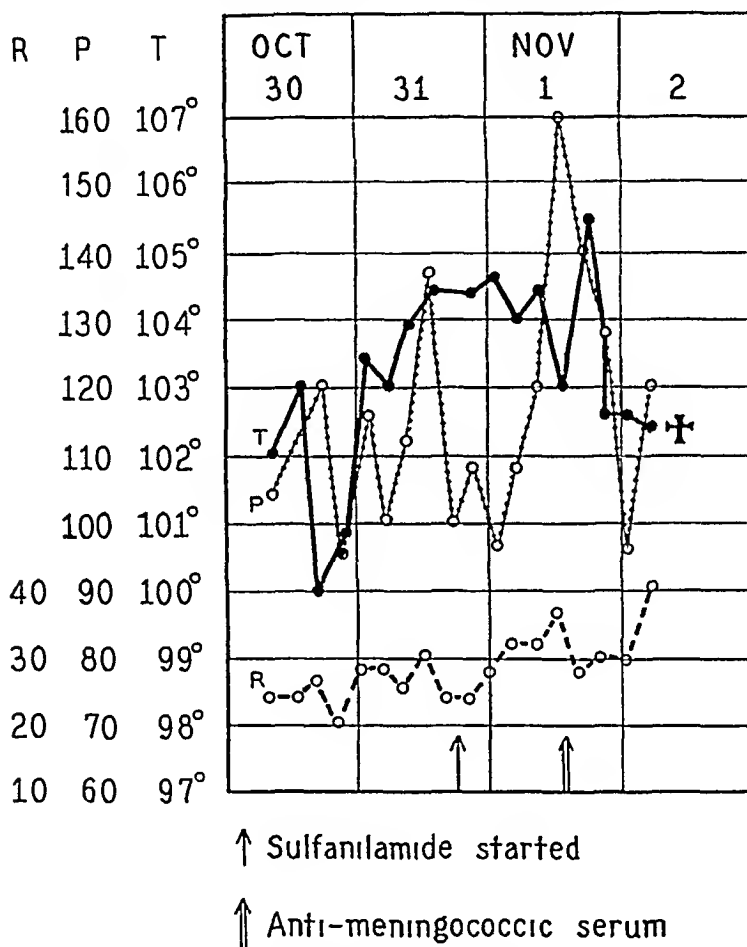


Fig 1—Record of respiratory rate, pulse rate and temperature in a case of Friedlander's bacillus septicemia and meningitis

tained many petechiae and was covered by a gelatinous purulent exudate. The serosa of about 4 feet (122 cm) of the midportion of the small intestine presented many hemorrhagic areas measuring 0.5 to 1 cm in diameter. The corresponding intestinal mucosa was riddled with shallow, soft hemorrhagic ulcers varying from 2 to 5 mm in diameter. The liver weighed 1,950 Gm and contained many small irregular yellowish opaque areas scattered over its surface and throughout its substance. These measured 2 to 5 mm in diameter. The spleen, pancreas and adrenals were not remarkable. The kidneys were enlarged, weighing 250 to 300 Gm. Their capsules were partially adherent, and both on the surface and throughout the kidney substance on section many small yellowish opaque lesions of the same type were seen (fig 2). There was no evidence of mucosal inflammation in the genitourinary tract. The

prostate was firm and irregular. After removal of the brain the meninges presented a slight diffuse haziness but no definite exudate. The vessels and nerves were normal, and the lateral sinuses were uninvolved.

Microscopic examination revealed the minute lesions of the myocardium, liver and kidneys to be miliary abscesses, some of which were also found in the pancreas and adrenals. They were composed of centers of necrotic material containing polymorphonuclear cells and fibrin surrounded by an acute exudate with some fibroblastic proliferation. An acute bronchitis was present but no notable pneumonitis. The intestinal ulcers presented an acute inflammatory appearance and were superficial, not involving the muscular layers. The kidney pelvis showed no inflammation. Carcinoma of the prostate was present. Sections of the brain revealed a diffuse acute purulent leptomeningitis with polymorphonuclear leukocytes predominating in the exudate. Some vessels within the brain were surrounded by groups of polymorphonuclear cells.

Cultures of the blood, meninges, bronchi and hepatic abscesses yielded an organism identical with the one isolated from the blood, urine and spinal fluid during life.



Fig. 2—Photograph showing embolic abscesses in the kidney

#### COMMENT

The portal by which the infection gained entry cannot be stated with certainty. Since the lesions observed in the urinary tract at autopsy appeared to be haematogenous, it was felt unlikely that the infection began there. Although the existence of a purulent bronchitis suggested the possibility of origin in the respiratory system, the history failed to substantiate this theory. In view of the extensive and rather unusual ulcerative lesions in the small intestine, it may be that the infection began as enteritis, with invasion of the blood stream resulting in embolic abscesses throughout the viscera and terminal meningitis. Banti<sup>4</sup> reported a fatal case of Friedlander's bacillus septicæmia, likewise without diarrhea, in which similar ulcerations were seen involving the colon and ileum.

<sup>4</sup> Banti, G. Sopra quattro nuove specie di protei o bacilli capsulati, *Sperimentale* 62 139 (Aug.) 1888.

## ANALYSIS OF THIRTY CASES OF FRIEDLANDER'S BACILLUS MENINGITIS

Meningitis due to Friedlander's bacillus is uncommon in the United States. Etiologic analysis of several large series of cases from various cities revealed that the meningitis was caused by Friedlander's bacillus in only 3 of a total of 3,714 cases. The case of Fothergill and Sweet<sup>5e</sup> is, to our knowledge, the only one of these which has been reported. Single instances of Friedlander's bacillus meningitis in this country have been described by Rothschild,<sup>6</sup> Gowen<sup>7</sup> and Kolmer and Rule.<sup>8</sup> In addition, Robertson has reported a case from Canada<sup>1a</sup> and Montes and Real<sup>1b</sup> 1 from Cuba. Most of the publications concerning this disease have appeared in European journals. The first case was recorded by Weichselbaum<sup>9</sup> (cited by Etienne<sup>10</sup>) only six years after Friedlander's original description of the organism, in 1882.

We have been able to collect data on 30 cases of meningitis caused by encapsulated bacilli of the Friedlander group, consisting of our own and 29 cases from the available literature, as listed in table 1. Since it appears from the work of Julianelle,<sup>11</sup> Edwards<sup>12</sup> and Osterman and Rettger<sup>13</sup> that Friedlander's bacillus and *Bacterium aerogenes* are closely related, if not indistinguishable, a few cases in which the disease was attributed to the latter organism are included.<sup>14</sup>

*Sex, Race and Age*—Of the 30 patients reported on, 19 were males and 8 females, and for 3 the sex was not stated. One patient was a Negro,<sup>6</sup> 2 were Chinese<sup>14c</sup> and the remainder were presumably of the white race. The age distribution is shown in table 2. On the basis of the age incidence observed by Neal in 1,496 cases of nontuberculous meningitis of all causes,<sup>5d</sup> the expected number for

5 (a) Holt, L. E. Observations on Three Hundred Cases of Acute Meningitis in Infants and Young Children, *Am J Dis Child* **1** 26 (Jan) 1911. (b) Dunn, C. H. Cerebrospinal Meningitis: Its Etiology, Diagnosis, Prognosis and Treatment, *ibid* **1** 95 (Feb) 1911. (c) Gilbert, R., and Coleman, M. B. Incidence of Various Species of Bacteria in Spinal Fluids from Cases of Meningitis, *J Lab & Clin Med* **13** 547 (Feb) 1928. (d) Neal, J. B. Experience of the Meningitis Division of the New York Department of Health, *Am J Pub Health* **21** 147 (Feb) 1931. (e) Fothergill, L. D., and Sweet, L. K. Meningitis in Infants and Children with Special Reference to Age Incidence and Bacteriological Diagnosis, *J Pediatr* **2** 696 (June) 1933.

6 Rothschild, K. Meningitis Caused by Friedlander's Bacillus, *J A M A* **97** 1956 (Dec 26) 1931.

7 Gowen, G. H. A Case of Friedlander's Bacillus Meningitis Secondary to Bilateral Otitis Media, *Illinois M J* **65** 533 (June) 1934.

8 Kolmer, J. A., and Rule, A. M. Sulfanilamide and Sulfapyridine in Treatment of B. Friedlander (*Klebsiella Pneumoniae*) Infections of Mice, *Proc Soc Exper Biol & Med* **42** 305 (Oct) 1939.

9 Weichselbaum, A. Ueber eine von einer Otitis media suppurativa ausgehende und durch den *Bac. pneumoniae* (Friedlander) bedingte Allgemeininfektion, *Monatschr f Ohrenh* **22** 200 and 229 (Aug) 1888.

10 Etienne, G. Le pneumobacille de Friedlander. Son rôle en pathologie, *Arch de méd exper et d'anat path* **7** 124, 1895.

11 Julianelle, L. A. Immunological Specificity of *Bact. Aerogenes* and Its Antigenic Relation to *Pneumococcus* Type II and Friedlander's Bacillus Type B, *J Immunol* **32** 21 (Jan) 1937.

12 Edwards, P. R. Relationships of the Encapsulated Bacilli with Special Reference to *Bact. Aerogenes*, *J Bact* **17** 339 (May) 1929.

13 Osterman, E., and Rettger, L. F. A Comparative Study of Organisms of the Friedlander and *Coli-Aerogenes* Groups, *J Bact* **42** 699 (Dec) 1941.

14 (a) Beitzke, H. Ueber einen Fall von Meningitis, verursacht durch *Bacterium lactis aerogenes*, *Centralbl f Bakt (Abt 1)* **37** 496, 1904. (b) Deane, A., and Shera, G. A Case of Infection of the Meninges by *Bacillus Lactis Aerogenes*, *Lancet* **2** 1237 (Dec 15) 1928. (c) Davis, L. J., and Fernando, F. S. Meningitis Due to Mucoid-Encapsulated Bacilli [case 1], *Tr Roy Soc Trop Med & Hyg* **29** 143 (July) 1935.

each of the three large age groups shown has been calculated and compared with that observed. Below the age of 3 years the incidence was about what might be expected. It should be mentioned that a large proportion of these patients (9 out of 11) were under 9 months of age. The age group from 3 to 20 years was

TABLE 1—*Thirty Cases of Friedlander's Bacillus Meningitis*

Published by	Year Published	Patient's		Probable Primary Focus	Other Extra meningeal Foci	Outcome
		Sex	Age			
Weichselbaum <sup>9</sup>	1888	F	54 yr	Otitis media	Mastoiditis, eustachian salpingitis, paranasal sinusitis	Death
Dmochowski <sup>15a</sup>	1894	M	54 yr	Sphenoid and maxillary sinusitis	Osteomyelitis of facial bones, phlegmon of face, brain abscess	Death
Etienne <sup>10</sup>	1895	M	33 yr	Pneumonia	Empyema, arthritis	Death, 6 days
Brunner <sup>21</sup>	1896	M	55 yr	Otitis	Petrositis, sinus thrombosis, embolic abscesses in kidneys	Death, 6 weeks
Jassniger <sup>16</sup>	1901	M	16 yr	Sphenoid sinusitis	Cavernous sinus phlebitis	Death, 7 days
Beitzke <sup>14a</sup>	1904	M	3 wk	Unknown	None found	Death, 18 days
Bonhoff and Esch <sup>23a</sup>	1912		New born	Otitis		Death, 14 days
Sredey, Lemaire and de Jong <sup>18</sup>	1912	M	26 yr	Pharyngitis	None found	Death, 12 days
Rénon and Blamoutier <sup>10</sup>	1921	F	44 yr	Otitis	Petrositis	Death
Elias, <sup>24a</sup> case 1	1924	M	62 days	Bronchitis?	Paravertebral pneumonia	Death
Menetrier and Bertrand Iontaine <sup>20</sup>	1924	M	33 yr	Unknown	None found	Death, 4 days
Lion and Minvielle <sup>24b</sup>	1924	M	38 yr	Pneumonia	Abscess of lung	Death, 23 days
Dufourt, Delattre and Bonnet <sup>17</sup>	1926		9 mo	Arthritis, ankle and elbow	None found	Death, 2½ mo
Papandrea, <sup>22</sup> case 1	1927	F	5 mo	Pneumonia	Pleuritis, pericarditis	Death, 26 days
Papandrea, <sup>22</sup> case 2	1927	M	2½ yr	Unknown	None found	Death, 5 days
Brain and Valentine <sup>25a</sup>	1928	M	22 yr	Otitis	Mastoiditis (postoperative)	Death, 22 days
Deane and Shera <sup>14b</sup>	1928	F	71 yr	Cholecystitis	None found	Death, 9 days
Rothschild <sup>6</sup>	1931	M	34 yr	Otitis	Mastoiditis, subdural abscess	Recovery
Comte, Levy Bruhl and Dany <sup>15</sup>	1931	M	50 yr	Unknown	None found	Death, 7 days
Fothergill and Sweet <sup>5e</sup>	1933	M	4 wk	Unknown	None found	Death
Gowen <sup>7</sup>	1934	F	63 yr	Otitis	Mastoiditis, abscesses in neck and arm	Death, 3 mo
Davis and Fernando, <sup>14c</sup> case 1	1935	F	29 yr	Uterine infection?	None found	Death, 9 days
Davis and Fernando, <sup>14c</sup> case 2	1935	M	1 mo	Unknown	Basal pneumonia (? terminal)	Death, 11 days
Leenhardt, Boucomont and Balmes <sup>24c</sup>	1937		4½ mo	Unknown	None found	Death, 8 days
Sieard and Pluvinage <sup>16b</sup>	1937	F	58 yr	Frontal sinusitis	Osteomyelitis frontal bone	Death, 4 weeks
Kolmer and Rule <sup>8</sup>	1939	M	36 yr	Frontal ethmoid and sphenoid sinusitis	None found	Death, 11 days
Slobozianu and Ionescu <sup>23b</sup>	1940	F	New born	Pneumonia	None found	Death, 4 days
Montes and Real <sup>1b</sup>	1940	M	2 yr	Unknown	None found	Recovery
Robertson <sup>1a</sup>	1941	M	49 yr	Maxillary sinusitis	? Bronchopneumonia	Recovery
Ransmeier and Major	1942	M	73 yr	Unknown	Bronchitis, enteritis, millary abscesses in viscera	Death, 5 days

surprisingly spared (14 patients expected, 1 observed), while a preponderance of the patients were adults (5 expected, 18 observed), many of them in the later decades of life. From this series it appears that Friedlander's bacillus meningitis, like other varieties, may occur in infants but is peculiar in that it tends to spare children over 3 years of age and has an unusual predilection for older adults.

*Probable Primary Focus*—The portal of entry for the infection is of the greatest interest but cannot always be established. The probable primary foci in 30 cases

are shown in tables 1 and 3. It will be noted that infections of the middle ear, mastoid and sinuses were found in over half the adults, while in the majority of the patients under 3 years of age the primary focus was unknown. Chronic disease of the ear and sinus of many years' duration may provide the avenue for invasion of the meninges in adults, while the sinuses are poorly developed in infancy and would not be expected to be of importance in that period of life. In 2 of the adults extremely severe sinusitis with osteomyelitis of the bony walls of the frontal and maxillary sinuses was observed,<sup>15</sup> while in 1 case the cavernous sinus was involved secondarily to sphenoid sinusitis.<sup>16</sup> Pneumonia was considered a precursor of Friedlander's bacillus meningitis in only 5 cases. Single cases in which the disease was probably secondary to cholecystitis,<sup>11b</sup> arthritis<sup>17</sup> and uterine infection

TABLE 2—Comparison of Age Incidence in 30 Cases of Friedlander's Bacillus Meningitis with that Observed in 1,496 Cases of Nontuberculous Meningitis of All Causes

Age Group	Cases of Nontuberculous Meningitis (Neal <sup>15a</sup> )		Friedlander's Bacillus Meningitis, Number of Cases	
	Number	Per Cent	Observed	Expected
Under 3 years	509	34	11	10.2
3 to 20 years	716	48	1	14.4
Over 20 years	271	18	18	5.4
Total	1,496	100	30	30.0

TABLE 3—Probable Primary Focus in 30 Cases of Friedlander's Bacillus Meningitis, According to Age\*

Probable Primary Focus	Number of Cases in Age Groups		
	Under 3 Years	16 to 73 Years	Total
Otitis, mastoiditis, etc	1	6	7
Paranasal sinusitis		5	5
Pneumonia, bronchitis	3	2	5
Pharyngitis		1	1
Cholecystitis		1	1
Arthritis	1		1
Uterine infection?		1	1
Unknown	6	3	9
Total	11	19	30

\* None of the patients were between 3 and 16 years of age

(Davis and Fernando,<sup>14c</sup> case 1) have been reported. Pharyngitis was thought to have been the primary focus in 1 instance.<sup>18</sup> Since it is known that Friedlander's bacillus may occasionally be isolated from the throat of a person with or without pharyngeal symptoms, it is conceivable that the organism may have entered through the pharynx in some cases in which the route of invasion has not been established.

15 (a) Dmochowski, Z. Beitrag zur Lehre über die pathogenen Eigenschaften des Friedlander'schen Pneumococcus, Zentralbl. f. Bakt. (Abt. 1) **15** 581 (April 27) 1894. (b) Sicard, A., and Pluvinage, R. Méningite à pneumobacilles de Friedlander, Presse méd. **45**: 1800 (Dec 15) 1937.

16 Jassniger, K. Der Pneumococcus Friedlander als Erreger der eitrigen Meningitis cerebrospinalis, Zentralbl. f. Bakt. (Abt. 1) **30** 1 (July 12) 1901.

17 Dufourt, A., Delattre and Bonnet. Meningite trainante à pneumo-bacille de Friedlander chez un nourrisson, Lyon méd. **138** 375 (Sept 26) 1926.

18 Siredey, A., Lemaire, H., and de Jong. Meningite cerebro-spinale à pneumo-bacille de Friedlander, Bull. et mem. Soc. méd. d. hôp. de Paris **34** 258 (July 26) 1912.



*Associated Complicating Conditions*—In the adult patients of Weichselbaum,<sup>9</sup> Renon and Blamoutier,<sup>19</sup> Rothschild<sup>6</sup> and Menetrier and Bertrand-Fontaine<sup>20</sup> sugar was found in the urine, while Robertson's patient<sup>1a</sup> was known to have diabetes. Brunner's patient<sup>21</sup> had cirrhosis of the liver, and autopsy of our patient showed carcinoma of the prostate. Some other patients were thought to have been alcoholic addicts. The infant patients of Beitzke<sup>11a</sup> and Papandrea<sup>22</sup> had congenital syphilis. Two newborn infants with the disease were found to have intracranial hemorrhages.<sup>23</sup> It seems likely that debilitating conditions may predispose to the development of Friedlander's bacillus meningitis.

*Diagnosis*—The usual signs and symptoms of meningitis are present in adults but may be lacking in infants. The diagnosis is a purely bacteriologic one and rests on the finding of the organism in smears and cultures of the spinal fluid. Of 19 cases of Friedlander's bacillus meningitis, including our own and others from the literature in which exact data were given, direct smears of the spinal fluid at the time of the first lumbar puncture were negative in 5 instances. Thus in about one fourth of these cases organisms were not found in the first smear. This fact is of considerable importance, since the failure to demonstrate organisms in smears of purulent spinal fluid when a diagnosis has not been made is usually considered strongly suggestive of meningococcic infection. Petechial hemorrhages occurring when Friedlander's bacillus septicemia is present may further confuse the picture, as in the case here reported. We have encountered 3 other cases of Friedlander's bacillus meningitis in which the initial diagnosis was uncertain enough so that antimeningococcus serum was given.<sup>24</sup> Cultures of the spinal fluid from the first lumbar tap were positive in 15 of 17 cases.

The spinal fluid is in no way characteristic, showing the usual changes of a purulent meningitis, with the cells in the exudate predominantly polymorphonuclear and an increased protein content and a diminished sugar content.

The demonstration of extrameningeal foci, such as otitis media, mastoiditis or sinusitis, may be suggestive if Friedlander's bacillus is shown to be the causative agent of such processes. Presence of the organism in cultures of material from the throat, of the urine or of the blood may supply additional evidence. Friedlander's bacilluria was observed in 1 fatal case<sup>25</sup> besides our own in which a blood culture

19 Renon, L, and Blamoutier, P. Un cas de meningite cerebrospinale a pneumobacille de Friedlander d'origine otitique, *Ann de med* **9** 119 (Feb) 1921.

20 Menetrier, P, and Bertrand-Fontaine. Sur un cas de meningite a pneumobacille du Friedlander a evolution suraigue, *Bull et mem Soc med d hôp de Paris* **48** 114 (Feb 1) 1924.

21 Brunner, C. Zur pathogenen Wirkung der Bacillus Friedlander. Ein Fall von acut metastasirender Allgemeininfektion nach Otitis media und Empyem des Proc mastoides, *Munchen med Wchnschr* **43** 286 (March 31) 1896.

22 Papandrea, F. Su due casi di meningite da diplobacillo di Friedlander, *Pediatrics* **35** 371, 1927.

23 (a) Bonhoff, H, and Esch, P. Ueber einen Fall von Meningitis purulente beim Neugeborenen infolge rechtseitiger eitriger Mittelohrentzündung, *Ztschr f Geburtsh u Gynak* **70** 886, 1912. (b) Slobozianu, H, and Ionescu, V T. La meningite apneumobacilles de Friedlander chez les nouveaux-nes, *Nourrisson* **28** 153 (July) 1940.

24 (a) Elias, F. Meningitis beim Saugling durch den Bacillus pneumoniae Friedlander [case 1], *Deutsche med Wchnschr* **50** 578 (May 2) 1924. (b) Lion, G, and Minvielle. Un cas de meningite suppuree a bacille du type Friedlander, *Bull et mem Soc med d hôp de Paris* **48** 286 (March 7) 1924. (c) Leenhardt, E, Boucomont, J, and Balmes, J. Deux cas de meningite a pneumobacille de Friedlander, *Arch Soc d sc med et biol, Montpellier* **18** 167 (April) 1937.

25 Comte, Levy-Bruhl, M, and Dany. Un cas de meningite a pneumobacille de Friedlander avec septicemie, *Bull et mem Soc med d hôp de Paris* **47** 139 (Feb 2) 1931.

was positive. We have found records of blood cultures of 10 patients with Friedlander's bacillus meningitis. Five of these, including the one here reported on, had positive cultures, and all these patients died.<sup>26</sup> Of the 5 with negative blood cultures 2 survived,<sup>27</sup> while a third, a 17 day old infant reported on by Elias<sup>24a</sup> (case 2), appeared on the way to recovery, only to die in a nursery outbreak of "influenzal pneumonia." The other 2 patients<sup>28</sup> died of meningitis, the first despite sulfapyridine therapy.

*Prognosis and Chemotherapy*—Friedlander's bacillus causes a particularly malignant type of meningitis, which until recently was almost always fatal. In the available literature published prior to the introduction of the sulfonamide drugs, Rothschild's case<sup>6</sup> is the only incontestable nonfatal case of purulent meningitis we have encountered in which Friedlander's bacillus was recovered from the spinal fluid and adequate details of its bacteriologic identification given. In this case meningitis was secondary to otitis media, mastoiditis and subdural abscess, with recovery after operation.

Since the advent of the sulfonamide compounds several patients with Friedlander's bacillus meningitis have been cured. Lombard and Mondzain-Lemaire<sup>29</sup> discussed a patient who apparently had a mixed meningeal infection after a head injury and recovered after treatment with sulfamidochrysoidine,<sup>30</sup> but the criteria for the bacteriologic diagnosis were not described. Robertson<sup>1a</sup> has recently reported a case in which a 49 year old man was cured with sulfapyridine. Friedlander's bacillus was found not only in the spinal fluid but in cultures of material from the throat and maxillary sinuses, and recovery of this patient is all the more remarkable because he had diabetes. Montes and Real<sup>1b</sup> described a Cuban child of 2 years without demonstrable primary focus who was likewise cured after administration of sulfapyridine. Both of these patients received autogenous vaccine late in the course of treatment. Kolmer and Rule<sup>8</sup> gave sulfapyridine unsuccessfully to an adult in whom the disease was secondary to Friedlander's bacillus infection of the sphenoid, ethmoid and frontal sinuses, but, although initial improvement was noted, cultures and smears of the spinal fluid continued positive. After five days a relapse occurred, and the patient died on the eighth day of treatment. Julianelle<sup>2a</sup> mentioned a case in which Friedlander's bacillus meningitis was cured with sulfadiazine, and Trevett, Nelson and Long<sup>2b</sup> briefly cited a case in which the disease was successfully treated by Hodes with the same drug.

Experimental studies on Friedlander's bacillus infections in animals have shown that sulfanilamide is practically ineffective against the organism, while sulfapyridine exerts a moderate activity.<sup>31</sup> Laboratory investigation suggests that

26 (a) Bram, W. R., and Valentine, F. S. O. A Case of Infection of the Meninges and Blood Stream by *Bacillus Mucosus Capsulatus*, *Lancet* **1** 855 (April 28) 1928. (b) Fothergill and Sweet<sup>5a</sup>. Sicard and Pluvinage<sup>15b</sup>. Comte, Levy-Bruhl and Dany<sup>25</sup>.

27 Robertson<sup>1a</sup>. Rothschild<sup>6</sup>.

28 Kolmer and Rule<sup>8</sup>. Leenhardt, Boucomont and Balmès<sup>24c</sup>.

29 Lombard, P., and Mondzain-Lemaire, S. Ménigite aigue, septique, post-traumatique. Traitement par sulfamido-chrysoidine. *Guerison*, *Mem Acad de chir* **64** 926 (June 15) 1938.

30 A compound supposedly identical with the original prontosil (a hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene).

31 (a) Gross, P., Cooper, F. B., and Lewis, M. Sulfanilamide Therapy of Friedlander's Infections of Mice, *Proc Soc Exper Biol & Med* **39** 12 (Oct) 1938. (b) Bliss, E. A., Feinstein, W. H., Garrett, A. W., and Long, P. H. Sulfapyridine and Sulfanilamide in Experimental Pneumococcal, Meningococcal, Welch Bacillary, and Friedlander's Bacillary Infections in Mice, *ibid* **40** 619 (April) 1939. (c) Kolmer and Rule<sup>8</sup>.

sulfadiazine surpasses its predecessors in the therapy of Friedlander's bacillus infections<sup>32</sup> The choice of the appropriate drug is thus of the greatest importance

If no organisms are found in smears of purulent spinal fluid from cases of undiagnosed meningitis, it would seem wise to use a drug with a wide range of action, such as sulfadiazine, since it may be effective against Friedlander's bacillus as well as against the meningococcus<sup>33</sup> and other more common causes of meningitis

#### SUMMARY

A case of Friedlander's bacillus septicemia and meningitis in an old man with carcinoma of the prostate has been reported, and autopsy observations are described The infection was so overwhelming that recovery could hardly have been expected, but the diagnosis was difficult and delayed and the treatment, accordingly misdirected, was not the best The case is of interest because of the rarity of Friedlander's bacillus as a cause of meningitis, and particularly in view of the small number of reports in the American literature The disease occurs chiefly in infants and in adults, often after the fourth decade of life Frequently it is associated with other debilitating conditions In occasional cases confusion with meningococcic meningitis may occur because of the presence of petechiae and the lack of organisms in smears of the spinal fluid A few patients with meningitis due to Friedlander's bacillus have recovered after administration of sulfapyridine or sulfadiazine, while formerly the condition was almost always fatal When the diagnosis is made or suspected vigorous treatment with one of these drugs is indicated Experimental work with animals suggests that sulfadiazine may prove more effective than its predecessors against Friedlander's bacillus infections

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32 Feinstein, W H, Williams, R D, Wolff, M S, Huntington, E, and Crossley, M L The Toxicity, Absorption, and Chemotherapeutic Activity of 2-Sulfanilamidopyrimidine (Sulfadiazine), *Bull Johns Hopkins Hosp* **67** 427 (Dec) 1940

33 (a) Dingle, J H, Thomas, L, and Morton, A R Treatment of Meningococcic Meningitis and Meningococcemia with Sulfadiazine, *J A M A* **116** 2666 (June 14) 1941  
Hodes, H L, and Strong, P S Treatment of Meningococcic Meningitis with Sulfonamides, *ibid* **119** 691 (June 27) 1942 Rundlett, E, Gnassi, A M, and Price, P Meningococcic Meningitis Prognostic Significance of the Spinal Fluid Sugar, *ibid* **119** 695 (June 27) 1942  
(b) Trevett, Nelson and Long<sup>2b</sup>

# SULFADIAZINE ADMINISTERED ALONE AND WITH ANTIPNEUMOCOCCUS SERUM IN THE TREAT- MENT OF PNEUMOCOCCIC PNEUMONIA

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Sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine), the pyrimidine analog of sulfapyridine, has been shown by Feinstone and his associates <sup>1</sup> in their experiments with mice to be less toxic than either sulfapyridine or sulfathiazole. They found the drug to be readily absorbed into the blood and rapidly excreted in the urine. Higher concentrations were obtained with sulfadiazine than with equivalent doses of sulfapyridine or sulfathiazole. Long and his co-workers <sup>2</sup> reported that sulfadiazine was less effective at equivalent concentrations than sulfathiazole in the treatment of experimental pneumococcic infections in mice. Osgood and Bullowa, <sup>3</sup> using tissue cultures, found sulfadiazine to be only one-quarter as effective against pneumococci as sulfapyridine and sulfathiazole in equivalent concentrations.

Studies on the action of sulfadiazine in human beings have been reported by various investigators <sup>4</sup>. With an associate we <sup>5</sup> have previously reported on the pharmacodynamics of the drug in man. It is well absorbed from the gastrointestinal tract. As a rule, most of the drug exists in the blood in the free form. It diffuses readily into the spinal, the pleural and the peritoneal fluid. Although the major portion of the drug is rapidly excreted in the urine, traces may be detected for as long as six days after ceasing administration. Approximately 65 per cent of the

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1 Feinstone, W. H., Williams, R. D., Wolfe, R. T., Huntington, E., and Crossley, M. L. The Toxicity, Absorption and Chemotherapeutic Activity of 2-Sulfanilamido-Pyrimidine (Sulfadiazine), *Bull. Johns Hopkins Hosp.* **67**: 427, 1940.

2 Long, P. H., Bliss, E. A., and Ott, E. Studies on Sulfadiazine, *Bull. Johns Hopkins Hosp.* **69**: 297, 1941.

3 Osgood, E. E., and Bullowa, J. G. M. Unpublished data.

4 (a) Plummer, N., and Ensworth, H. K. Absorption and Excretion of Sulfadiazine, *Proc. Soc. Exper. Biol. & Med.* **45**: 734, 1940. (b) Reinhold, J. G., Flippin, H. F., Schwartz, L., and Domm, A. H. Absorption, Distribution and Excretion of 2-Sulfanilamido Pyrimidine (Sulfapyridine, Sulfadiazine) in Man, *Am. J. M. Sc.* **201**: 106, 1941. (c) Peterson, O. L., Strauss, E., Taylor, F. H. L., and Finland, M. Absorption, Excretion and Distribution of Sulfadiazine (2-Sulfanilamido-Pyrimidine), *ibid.* **201**: 357, 1941. (d) Sadusk, J. F., Jr., and Tredway, J. B. Observations on Absorption, Excretion, Diffusion and Acetylation of Sulfadiazine in Man, *Yale J. Biol. & Med.* **13**: 539, 1941. (e) Wheeler, C., and Plummer, N. Sulfadiazine and Sodium Sulfadiazine. A Comparison of Certain of Their Clinical and Pharmacological Values, *Ann. Int. Med.* **16**: 269, 1942.

5 Ratish, H. D., Shackman, N. H., and Bullowa, J. G. M. The Pharmacodynamics of Sulfadiazine in Man, *New England J. Med.* **226**: 596, 1942.

dose given may be recovered from the urine, and about one third of this is conjugated. High concentrations in the blood may be obtained rapidly by intravenous, subcutaneous and intramuscular administration of the sodium salt. Sulfadiazine is less toxic than either sulfapyridine or sulfathiazole.

#### METHOD AND MATERIAL

We report herewith our experience with 232 patients with pneumococcal pneumonia treated with sulfadiazine and 70 patients with this condition treated with rabbit antipneumococcus serum in addition. These patients, admitted to the Pneumonia Service of Harlem Hospital from July 1, 1940 to June 30, 1941, were adults for whom the diagnosis of pneumonia was based on history and physical findings and confirmed by roentgen examination. Prior to the institution of therapy bacteriologic studies of the sputum and the blood were made in all cases, and ordinarily treatment was withheld until the type of pneumococcus was determined. However, when attempts at typing the pneumococcus had been unsuccessful for twenty-four hours, therapy was no longer withheld, and sulfadiazine was given.

*Dose*—Most of the patients in this series received an initial dose of 4 or 5 Gm of sulfadiazine followed by a dose of 1 Gm every four or six hours. Some patients, those very ill, received an initial intravenous injection of 5 Gm of sodium sulfadiazine followed by doses of 1 Gm given orally or intravenously at four or six hour intervals. The administration of the drug was discontinued when the temperature fell and remained below 100 F with a pulse rate below 90 per minute for eighteen to twenty-four hours. Sulfadiazine was not given again unless there was a substantial persistent rise in temperature. Forty-four patients, or 63 per cent, received serum and sulfadiazine simultaneously, 9 patients received them one day apart, and 17 of the patients received the therapeutic agents two or more days apart. Of the 17 patients, 10 received serum first, whereas 7 were given the drug before the serum. Of the patients who received serum first, 8 were given sulfadiazine in addition either because the serum failed to influence the course of the disease or because the temperature, having fallen to normal, rose. Six patients who received the drug first were given serum because of marked bacterial invasion of the blood.

Samples of blood for determining drug levels and making immunologic studies were drawn every two days or more frequently if indicated. Concentrations of sulfadiazine were determined by the method of Bratton and Marshall, using a photoelectric colorimeter.<sup>6</sup>

#### RESULTS

*Patients Who Died*—Table 1 shows the gross mortality without taking into consideration the essential factors influencing it, such as age and day of illness on which therapy was begun. Of the 232 patients treated with sulfadiazine alone 31 died—a mortality of 13.4 per cent. Excluding those patients moribund on admission who died within twenty-four hours, the mortality is 8.3 per cent. Nine of 29 patients, or 31 per cent, with bacteremia died. Of these, 6 died within twenty-four hours, and when they are excluded, the mortality becomes 13 per cent. The total mortality for the patients undergoing combination therapy was 14.3 per cent. Only 1 patient, with bacteremia, died within twenty-four hours of admission to the hospital. The mortality for patients with bacteremia in this group was 22.2 per cent. Although this was lower than the total mortality for patients with bacteremia in the group treated with sulfadiazine alone, the difference is not in itself significant. The incidence of blood cultures positive for pneumococci among patients given both serum and sulfadiazine was twice as great as among patients given sulfadiazine alone. This is a statistically significant difference ( $R D E = 2.5$ ).<sup>7</sup>

6 Bratton, A. C., and Marshall, E. K., Jr. New Coupling Component for Sulfanilamide Determination, *J. Biol. Chem.* **128**: 537, 1939.

7 The abbreviation  $R D E$  signifies the ratio of difference to error. A figure of 2.0 or more indicates significance.

The most frequently encountered *Pneumococcus* in both groups was type III, which caused 42 of 232 infections (18 per cent) in patients treated with sulfadiazine alone and 20 of 70 infections (28.6 per cent) in patients given combined therapy. *Pneumococcus* type VII was next in frequency, accounting for 11.6 and 14.3 per cent of infections, respectively. Next in order of frequency were pneumococci of type I, type IV and type VIII. Of these most frequently encountered types in the sulfadiazine-treated group, *Pneumococcus* type IV showed the highest mortality, with 21 per cent (4 of 19), followed by *Pneumococcus* type I (17.4 per cent), *Pneumococcus* type III (16.6 per cent) and *Pneumococcus* type VIII (6.3 per cent). In the group given both sulfadiazine and serum 1 of 5, or 20 per cent, of the patients whose infecting organism was *Pneumococcus* type I or type III died. Of the patients with infection caused by *Pneumococcus* type VIII, 14.3 per cent (1 of 7) died. The lowest mortality among the more frequently occurring

TABLE 1—*Analysis of Infections by Types of Causative Pneumococci*

Type of <i>Pneumococcus</i>	Treatment					
	Sulfadiazine			Sulfadiazine + Serum		
	No of Patients	No of Deaths	Percentage of Deaths	No of Patients	No of Deaths	Percentage of Deaths
I	23 9*	4 2*	17.4 22.2*	5 3*	1 0*	20.0 0.0*
II	7 1*	0 0*	0.0 0.0*	4 3*	1 1*	25.0 33.3*
III	42 2*	7 2*	16.6 100.0*	20 2*	4 2*	20.0 100.0*
IV	19 6*	4 2*	21.0 33.3*	4 1*	0 0*	0.0 0.0*
V	5 0*	0 0*	0.0 0.0*	2 1*	0 0*	0.0 0.0*
VI	3 0*	1 0*	33.3 0.0*			
VII	27 3*	2 1*	7.4 33.3*	10 2*	0 0*	0.0 0.0*
VIII	16 1*	1 1*	6.3 100.0*	7 1*	1 0*	14.3 0.0*
Other types	99 7*	12 1*	13.3 14.3*	18 5*	3 1*	16.6 20.0*
Total	232 29*	31 9*	13.4 31.0*	70 18*	10 4*	14.3 22.2*
Total minus deaths in 24 hours	217 23*	18 3*	8.3 13.0*	69 17*	9 3*	13.0 17.6*

\* Bacteremia

types in this study was in infections caused by *Pneumococcus* type VII in the group given both sulfadiazine and serum and by *Pneumococcus* type VIII in the group given only sulfadiazine. Among the patients with type II pneumococcus pneumonia, which is usually a severe infection, there were no deaths in the sulfadiazine-treated group of 7 patients and only in the group of 4 patients undergoing combined therapy, although 3 of these 4 patients were bacteremic.

Among the numerous factors that influence the prognosis for patients with pneumonia is the presence of specific soluble substance<sup>8</sup> in the blood. Eight patients in the sulfadiazine-treated group and 7 patients in the group given both sulfadiazine and serum had capsular carbohydrate in their blood (table 2). *Pneumococcus* type III was the most frequently occurring type in both groups. Approximately one half of the patients in both groups died. In the drug-treated group

<sup>8</sup> This substance may also be referred to as capsular carbohydrate or capsular polysaccharide.

3 of the 4 patients who died had infections caused by *Pneumococcus* type III. One patient (1), a 38 year old Negro, was admitted on the sixth day of illness with signs of meningeal irritation in addition to pneumonia (spinal fluid was normal). The next day he became irrational and went into shock. He received a total of 17 Gm of sulfadiazine. The concentration of the drug in the blood

TABLE 2— *pertinent Data on Patients with Capsular Carbohydrate in Their Blood*

Case No and Age	Type of Cause and Pneumococcus	Day of Illness		Blood Culture *	Day of Illness S S S † Detected	Treatment		Rabbit Serum Units	Pre cipitin Test	Comment	Outcome
		Ad mitted to Hos pital	Ther apy Begun			Total Dose of Sulfa diazine, Gm	Blood Level, Mg % Free Drug				
1, 38	III	6	6	Nega tive	8	17	5.2 8.5		Nega tive		Died
2, 69	III	?	?	Nega tive	?	39	11.3 13.8 11.8			Cardiac disease	Died
3, 50	III	10	11	Posi tive		7.5	Not de termined		Nega tive	Colostomy for lympho granuloma venereum	Died
4, 50	VIII	5	5	Posi tive		1	Not de termined		Not done	Sterile effusion	Died
5, 29	XVI	5	6	Nega tive	8	40	6.6 7.9 6.7		Posi tive 1.4		Recovered
6, 62	VIII	3		Nega tive	8	15	5.1		Not done		Recovered
7, 25	I	4	4	Posi tive	7	33	6.6 9.5		Posi tive, 1.4		Recovered
8, 15	II	3	3	Nega tive	4	12	3.8 3.5 5.5		Not done		Recovered
9, 56	III	?	?	Posi tive	?	4	Not de termined	560,000	Not done	Hypertensive heart disease rectal stricture hepatitis	Died
10, 60	III	9 (?)	9 (?)	Posi tive	10	6	Not de termined	245,000	Not done		Died
11, 50	III	9 (?)	10 (?)	Not done		39	5.8 6.1	431,000	Nega tive		Died
12, 42	VIII	9	11	Not done	10	21	9.0 14.0	331,750	Not done		Died
13, 43	VII	1	3	Posi tive	10, 11, 12, 16	26	5.2 10.4 7.7 7.0	243,000	Ample	Sterile effusion	Recovered
14, 27	XIX	3	3	Posi tive	3, 4, 5, 6	57	7.5 10.9 10.1 13.0	297,500	Posi tive 1.4		Recovered
15, 16	V	?	?	Posi tive	?	77	5.0 6.8 7.3 9.6 7.1 3.9 2.8 3.4	520,000	Not done	Pericardial effusion	Recovered

\* Negative (or positive) for pneumococci

† Specific soluble substance

on two occasions was 5.2 and 8.5 mg per hundred cubic centimeters. He died on the fourth day of hospitalization. A second patient (2), a 69 year old man, for whom the date of onset of illness was unknown, received 39 Gm of sulfadiazine, the concentration of the drug in the blood reached 14.8 mg per hundred cubic centimeters. His blood was sterile on culture but gave a strong reaction for capsular carbohydrate. He became stuporous, and his cardiac rhythm became irregular and rapid. Although he seemed to respond well to digitalis, he died

eight days after admission to the hospital. His infection had not been controlled (the temperature remained elevated) in spite of adequate concentrations of sulfadiazine. The third patient with an infection caused by *Pneumococcus* type III (patient 3) was a 50 year old woman who in addition to pneumonia had had a colostomy done for lymphogranuloma venereum and was admitted in an emaciated state. Her blood contained pneumococci of type III as well as capsular carbohydrate. She received only 7.5 Gm of sulfadiazine. The fourth patient (4) in the drug-treated group was a 50 year old man with bacteremia due to *Pneumococcus* type VIII and a sterile pleural effusion. Blood cultures were positive for the infecting organism on several occasions. He received only 4 Gm of sulfadiazine and died thirty-two hours after admission. The 4 patients in this group who recovered had infections due to *Pneumococcus* type I, type II, type VIII and type XVI respectively. They were less severely ill than those who died. All but 1 were under 40 years of age, 3 of the 4 were admitted prior to the fifth day of their illness. All but the patient with the infection due to *Pneumococcus* type I had blood cultures negative for pneumococci.

Of the 7 patients in the group given both sulfadiazine and serum who had capsular carbohydrate in their blood, 4 died, 3 of these 4 patients (9, 10 and 11) had infections caused by *Pneumococcus* type III. All 3 were over 40 years of age, and therapy was begun late in the course of their illness. Two of them had bacterial invasion of the blood. One died three hours and another seven hours after therapy was started and had received only 4 and 6 Gm of sulfadiazine, respectively, in addition to serum. The third patient received 39 Gm of the drug and 431,000 units of rabbit serum. Two died too soon to permit blood levels of sulfadiazine to be determined, the third had a blood level of 6.1 mg of free drug per hundred cubic centimeters. The fourth patient who died (patient 12) was a 42 year old woman with an infection due to *Pneumococcus* type VIII, for which therapy was begun on the ninth day of illness. The blood of 1 of the 4 patients who died was studied for precipitins, and none was found. The 3 patients in this group who recovered had infections due to *Pneumococcus* type V, type VII and type XIX, respectively. All had blood cultures positive for the infecting organism. Two of the 3 had precipitins in their blood after serum therapy.

All patients with infections due to *Pneumococcus* type III whose blood gave a reaction for specific soluble substance died regardless of the form of therapy. Three of these 6 patients had bacteremia as well. Six of a total of 15, or 40 per cent, of those patients who had demonstrable specific soluble substance in their blood had infections due to the type III pneumococcus. This pneumococcus accounted for 6 of the 8 deaths. That *Pneumococcus* type III produces capsular carbohydrate more abundantly than pneumococci of other types and that the presence of this substance in the blood of patients is of grave prognostic import has been previously shown in reports from this laboratory (Bukantz and associates<sup>9</sup>). The death rate among patients with detectable specific soluble substance in their blood is approximately four times greater than among those patients who do not have it.

An analysis of death rates in relation to age and to day of illness on which therapy was instituted is shown in table 3. In both therapy groups the largest mortality occurred in patients over 40 years of age first treated after the fifth day of illness, the mortality was about twice that for any of the three other categories in table 3. This last category contained the largest number of patients in both therapy groups — 40 per cent in the drug-treated group (93 of 232) and 34 per cent in the group given both sulfadiazine and serum (24 of 70).

<sup>9</sup> Bukantz, S. C., de Gara, P. F., and Bullowa, J. G. M. Capsular Polysaccharide in the Blood of Patients with Pneumococcic Pneumonia, *Arch. Int. Med.* **69** 191 (Feb.) 1942.



Detailed case analyses for the patients who died are shown in tables 4 and 5. It will be seen that a number of the patients in both therapy groups died not of their pulmonary infection but of other unrelated conditions in which the pneumonia was a terminating event. In the sulfadiazine-treated group (table 4), 1 patient (26) had a coronary occlusion preceding pneumonia, and lobar pneumonia developed in another (patient 37) one day after a gastric resection for carcinoma. One patient (22) was admitted after an acute cerebral hemorrhage with a right hemiplegia, and pneumonia developed six days later; he died within twenty-four hours after institution of therapy. Still another patient (32) had a carcinoma of the esophagus. In patient 34 the complicating factor was severe scleroderma. Nine patients had cardiac disease of various degree, causation and duration. Of these, 2 patients were in mild congestive failure on admission to the hospital; of the remainder, 5 had diminution of cardiac reserve, such as dyspnea on effort, which contributed to the fatal outcome.

*Patients Who Recovered*—In addition to the effect of a given therapeutic agent on the mortality of a disease, one must consider also its effect on the clinical course of the disease in the patients who recovered. In the sulfadiazine-treated group

TABLE 3—*Relation of Age, Day of Illness on Which Therapy Was Started and Outcome*

	Treatment					
	Sulfadiazine			Sulfadiazine + Serum		
	No. of Patients	No. of Deaths	Percentage of Deaths	No. of Patients	No. of Deaths	Percentage of Deaths
Patients under 40, first treated on 1st to 4th day of illness	33 5*	1 0*	3.0 0.0*	9 3*	0 0*	0.0 0.0*
Patients under 40, first treated on 5th day of illness and later	66 7*	5 2*	7.6 28.6*	19 3*	1 0*	5.3 0.0*
Patients over 40, first treated on 1st to 4th day of illness	10 5*	5 1*	12.5 20.0*	18 5*	2 0*	11.1 0.0*
Patients over 40, first treated on 5th day of illness and later	93 12*	20 6*	21.5 50.0*	24 7*	7 4*	29.3 57.2*

\* Bacteremia

54 of 201 patients who recovered, or 26.9 per cent, had their disease terminated within twenty-four hours after the institution of therapy, with a fall in temperature below 100 F and in pulse rate below 90 per minute as a criterion for the termination of the infection. Of the patients who recovered 118 of 201, or 58.7 per cent, became afebrile within forty-eight hours after receiving the first dose of sulfadiazine. The temperature and the pulse rate fell to normal in relation to the administration of the drug and not to the day of illness on which therapy was started. Of the patients who received both serum and sulfadiazine, 26 of the 60 who recovered, or 43 per cent, became afebrile within forty-eight hours after therapy was started.

In the drug-treated group the median dose of sulfadiazine for the patients who recovered was 20.7 Gm. Of these patients, 63 per cent received between 10 and 24 Gm of sulfadiazine, whereas 34 per cent of those who died were in this dose range. There were 28 patients who received less than 10 Gm of sulfadiazine, 12 of these recovered, and 16 died—this represents 6 per cent of the recoveries and 52 per cent of the deaths. The patients who received this dose group and who died were much more severely ill on admission than were the 12 who recovered—50 per cent of the former had bacteremia but none of the latter. Most of those who received less than 10 Gm of the drug and died did so within twenty-four hours after therapy was begun.

TABLE 4—Case Analyses of Deaths Occurring Among Patients Treated with Sulfadiazine

No of Patient	Type of Pneumo coccus	Age, Sex	Day of Illness on Which Therapy Started	Interval Between Beginning of Therapy and Death	Blood Culture *	S S S † in Blood	Total Dose of Sulfadiazine, Gm	Complications and Associated Conditions
16	I	67 ♀	6	13 hr	Positive	Negative	8	
17	I	43 ♂	3	3 hr	Positive	Not done	4	Cardiac decompensation pulmonary edema
18	I	39 ♂	4	12 days	Negative	Negative	35 5	
19	I	78 ♀	7	19 days	Negative	Negative	21	Empyema, second degree burns
2	III	67 ♂	?	7 days	Negative	Positive	39	Cardiac disease
20	III	65 ♀	3	17 days	Negative	Negative	28	Pleural effusion, traumatic pneumothorax, hypertensive heart disease, adenoma of thyroid
21	III	65 ♀	? Late	28 hr	Positive	Not done	8	Autopsy cholecystitis, atheroma of aorta, myocardial fibrosis, fatty metamorphosis of liver, chronic pyelonephritis
1	III	38 ♂	6	60 hr	Negative	Positive	17	Epilepsy
22	III	75 ♂	? Late	11 hr	Negative	Negative	7	Hypertensive and arteriosclerotic heart disease, cerebral hemorrhage
23	III	32 ♀	? Late	14 hr	Negative	Not done	6	Coma on admission, asthmatic bronchitis
3	III	50 ♀	11	36 hr	Positive	Positive	7 5	Autopsy esophageal varices, chronic duodenal ulcers, colostomy for lymphogranuloma venereum
24	IV	62 ♂	?	7 hr	Positive	Negative	6	Autopsy fibrinous pleurisy cirrhosis of liver, cloudy swelling of kidney coronary and aortic atherosclerosis
25	IV	52 ♀	15	10 hr	Positive	Negative	6	Treatment begun late in course of illness
26	IV	65 ♀	?	10 hr	Not done	Not done	7	Coronary occlusion
27	IV	53 ♀	?	36 hr	Negative	Negative	14	Effusion
28	VI	65 ♀	?	9 days	Negative	Negative	18	Emphysema, chronic bronchitis, coronary disease decubitus ulcers
29	VII	32 ♀	6	26 hr	Positive 6 times	Negative	10	Overwhelming bacteremia
30	VII	33 ♀	?	12 hr	Negative	Negative	9	
4	VIII	50 ♂	3	3 hr	Positive	Positive	4	Sterile effusion avitaminosis
31	IX	54 ♂	10	46 hr	Negative	Negative	13	Putrid empyema secondary to ruptured pulmonary abscess
32	IX	64 ♂	?	35 hr	Negative	Negative	14	Carcinoma of esophagus
33	X	64 ♀	?	8 days	Negative	Not done	14	
34	XI	49 ♀	4	49 hr	Negative	Negative	16	Scleroderma Addison's disease ?
35	XII	50 ♀	9	4½ days		Negative	18	Cardiac disease
36	XXI	43 ♂	?	13½ days	Negative	Negative	28	Hypertensive cardiovascular disease
37	XXV	45 ♂	?	96 hr			7	Complication after operation for carcinoma of stomach
38	XXXIII	48 ♀	14	5 hr	Negative	Not done	4	Hepatomegaly, cause unknown
39	XXXIV	63 ♂	14	15 hr	Negative	Not done	7	Delirium tremens, autopsy syphilitic aortitis, fatty degeneration of liver, coronary atherosclerosis
40	XVIII A	38 ♂	5	3 hr	Positive	Not done	6	Rheumatic heart disease
41	III B F A	45 ♂	3 ?	16 hr	Negative	B F A ‡	8	Autopsy fibrinous pleurisy, fatty metamorphosis of kidney, benign nephrosclerosis
42	VIII XXXIV	69 ♀	4	25 hr	Negative	Negative	10	Autopsy purulent empyema, fibrinous pericarditis

\* Positive (or negative) for pneumococci

† Specific soluble substance

‡ Bacillus Friedlander A

Many variables are involved which do not easily lend themselves to evaluation, so that one cannot arbitrarily state what constitutes the optimum dose. The virulence of the organisms and their susceptibility to the drug, inhibiting or enhancing substances in the blood, the number of bacteria in the local lesion, bacterial invasion of the blood and complications are but a few of the factors involved. We may, however, suggest that 10 Gm of sulfadiazine is, in the majority of cases, insufficient to control pneumococcic pneumonia and that doses of 10 to 24 Gm are adequate for two thirds of patients with such pneumonia.

In attempting to determine an adequate therapeutic concentration of the drug in the blood similar difficulties are encountered. There is great variability in the blood levels obtained with the same dose of drug in different patients and

TABLE 5—*Case Analyses of Deaths Occurring Among Patients Treated with Sulfadiazine and Serum*

No of Patient	Type of Pneumococcus	Age Sex	Day of Illness		Interval Between Therapy and Death	Blood Culture *	S S in Blood	Total Dose of Sulfadiazine Gm	Total Dose of Serum, Units	Pre eliptin Test	Complications and Associated Conditions
			Sulfadiazine Therapy Started	Serum Given							
43	I	74 ♂	23	23	29 hr		Negative	6	214,500	Not done	Admitted in state of pulmonary edema
44	II	41 ♂	13	7	17 days	Positive	Negative	47 10	200,000	Positive	Treatment begun late in course of illness
45	III	40 ♂	3	3	9 days	Negative	Negative	47	850,000	Positive	
10	III	63 ♀	9	9	7 hr	Positive	Positive	6	245,000	Not done	Inadequate late treatment
11	III	50 ♂	9	10	7 days		Positive	39	431,000	Negative	Azotemia
9	III	56 ♀	?	?	3 hr	Positive	Positive	4	300,000	Negative	Arteriosclerosis hypertensive heart disease, hepatitis lymphogranuloma venereum with rectal stricture
12	VIII	42 ♀	9	11	4 days	Negative	Positive	21	334,750	Not done	Treatment begun late in course of illness
46	XXXIII	49 ♂	5	6	31 hr	Positive	Negative	10	205,000	Not done	Circulatory failure
47	XXXIII	36 ♀	8	8	61 hr	Negative	Negative	16	150,000	Positive	Treatment begun late in course of illness
48	XXIII B F A †	46 ♂	3	3	32 hr	Negative	Negative	12	120 cc B F A serum	Not done	Autopsy hepato megalia fibrinous pleurisy atherosclerosis of aorta chronic myocarditis

\* Positive (or negative) for pneumococci

† Specific soluble substance

‡ Bacillus Friedlander A

in the same patient at different times—age and degree of absorption, conjugation and renal elimination are some of the factors influencing blood levels. In addition, pneumococci, even of the same type, vary in susceptibility to a given sulfonamide compound (as shown by in vitro experiments). In the sulfadiazine-treated group the largest number of patients who recovered had a blood level between 7 and 8 mg of free drug per hundred cubic centimeters as their highest concentration. Of the patients who recovered (125 of 201), 62 per cent had blood levels ranging from 5 to 10 mg of free drug per hundred cubic centimeters, whereas 34 per cent of the patients who died had the same concentration range. The median of the highest concentration of all the patients who recovered was 87 mg per hundred cubic centimeters. The median initial concentration among the patients who recovered was 74 mg per hundred cubic centimeters. In 24 per cent of the

total number of patients in the sulfadiazine-treated group (55 of 232) the initial concentration was the highest

In the group given both sulfadiazine and serum there were 6 patients whose blood was not studied, so that observations are based on the remaining 4. The median highest concentration in the 58 patients who recovered was 8.4 mg per hundred cubic centimeters. Of these patients, 62 per cent had blood levels of free drug ranging from 6 to 10 mg per hundred cubic centimeters, 3 of the 7 patients who died had the same concentration range.

*Rises in Temperature*—In 167 of 201, or 83 per cent, of the patients who recovered after treatment with sulfadiazine alone the temperature and the pulse remained down after administration of the drug had been discontinued. Thirty-four patients had a rise in temperature after it had remained below 100 F for about twenty-four hours. The temperatures of 5 of the 32 patients whose temperature charts were analyzed rose while they were still receiving the drug, the temperatures of the remaining patients rose after administration of sulfadiazine had been stopped. The shortest interval between discontinuance of the drug and rise in temperature was eight hours, the longest, fourteen days. Most (24 of 32) of the secondary rises in temperature occurred within seventy-two hours after sulfadiazine therapy had been discontinued. Four patients had a rise in temperature on one observation only, whereas the remainder had a sustained temperature for a period varying from eight hours to eleven days. In more than half the patients the temperature fell within forty-eight hours after it had risen. Seven patients had more than one bout of fever, with normal temperature between. Most of the febrile episodes were relatively mild, only 7 patients had temperatures above 102 F. Sulfadiazine was readministered to only 4 patients. The additional sulfadiazine was not especially effective, only 1 patient showed a prompt fall in temperature. It was found that 3 patients had sterile pleural effusions, 1 had sinusitis and another had purulent conjunctivitis. In the case of 2 others administration of the drug was discontinued while the temperature and the pulse were still elevated. No explanation could be found for the rise in temperature of the remaining 25 patients.

In the group given both sulfadiazine and serum 16 patients, or 27 per cent, had a rise in temperature, in 2 of these the rise occurred during the administration of the drug but after the serum had been given. The interval between discontinuance of therapy (drug) and rise in temperature varied from twelve hours to eleven days. In 50 per cent of the patients the febrile episode occurred within forty-eight hours after cessation of therapy. Seven patients had more than one febrile period, with normal temperature intervening. Temperatures above 102 F occurred in 10 patients. The temperature remained elevated from eight hours to nineteen days, and in half the patients the elevation lasted for more than four days. One patient was given additional drug for four days without effecting a drop in temperature. Sterile fluid was obtained by thoracentesis several days later. The febrile reactions were due to sterile effusion in 2 instances and to serum sickness in 5. Spread of the infection to another lobe, as well as development of sterile fluid on the side of the original infection, was the cause of the rise in temperature in 1 patient (49, fig. 1). In another patient concomitant tuberculosis was responsible for the febrile period. In 2 patients infection of the urinary tract due to *Escherichia coli* was the probable cause. The rise in temperature of the remaining 5 patients in the group could not be explained.

It is of interest to note that 30 per cent of the febrile episodes in the sulfadiazine-treated group and 50 per cent of those in the group given both sulfadiazine and



effusion was discovered during treatment. All the patients in both groups who recovered had blood cultures positive for the infecting pneumococcus, whereas those who died did not have bacterial invasion.

One of the sulfadiazine-treated patients who died (patient 19) was a 78 year old Negress who was admitted on the fifth day of her illness with a type I pneumococcus lobar pneumonia and effusion. Repeated thoracic taps yielded purulent fluid from which the pneumococcus grew. In addition, she had second degree burns of the right side of the chest and abdomen and the right thigh. Because of her age and debility she was treated by repeated aspirations and instillation of sulfadiazine into the pleural cavity, she also received the drug orally. Specific soluble substance was detected in the thoracic fluid but not in her blood. The blood, tested on one occasion, did not show precipitins. After apparent improvement the patient died in shock nineteen days after admission to the hospital.

The second patient (42) was a 69 year old emaciated Negress admitted on the third day of her infection, she died forty-eight hours later. A diagnosis of pneumonia of the lower lobe of the right lung was made on admission, and Pneumococci of type VIII and type XXXIV were recovered from the sputum. A clinical impression of enlargement of the heart was confirmed by roentgen examination. Fluid in the chest was not suspected ante mortem. At autopsy 200 cc of purulent exudate in the right pleural cavity, fibrinous pericarditis and cardiac hypertrophy were encountered.

The third patient (27), a 53 year old Negress, was brought to the hospital after three weeks of illness at home. Pleural effusion was found on admission, and thoracentesis yielded serosanguineous fluid from which Pneumococcus type IV was isolated. The patient received a total of 14 Gm of sulfadiazine by mouth, the concentration of free drug in the blood was 5.6 mg per hundred cubic centimeters on one occasion. The patient was dehydrated. She became semicomatose and died eighty-four hours after admission.

One of the patients (50) in the sulfadiazine-treated group who recovered was a 39 year old man admitted on the second day of his disease with a type VII pneumococcus pneumonia and a blood culture positive for the infecting organism. The organism was recovered from his thoracic fluid on several occasions, capsular polysaccharide was detected once in the fluid. In addition to 47 Gm of sulfadiazine given orally, he received 15 Gm of the drug in divided doses by pleural injection. Precipitins were found in his blood on several occasions. He made an uneventful recovery without surgical intervention and was discharged cured thirty-five days after admission to the hospital. His blood picture will be discussed in another portion of this paper.

The other recovery in this group was made by a patient (51) with type I pneumococcus empyema who had had a rib resection performed fourteen days after admission. His blood culture was positive for Pneumococcus type I on one occasion. Prior to thoracotomy he had received 19 Gm of sulfadiazine, but none after it. His temperature dropped to normal on the third day after operation. Recovery was uneventful.

The 2 patients with empyema who received serum and sulfadiazine had infections due to type IV and type VII organisms, respectively. Both had bacterial invasion of their blood. They had ample circulating antibodies in the blood, but neither had had capsular polysaccharide in the blood or the thoracic fluid. The patient with the type IV pneumococcus infection (patient 52) was admitted on the fourth day of his infection, and the presence of fluid in his chest was suspected

five days later. Numerous attempts at thoracentesis were unsuccessful. Because of roentgen evidence thoracotomy was performed one month after admission and a paravertebral empyema on the right side was found. Prior to the operation the patient received 36 Gm of sulfadiazine and 620,000 U S P units of rabbit anti-pneumococcus serum. His temperature fell to normal on the first day after operation, and he was discharged thirty days later.

The other patient (53), a 33 year old man, was admitted two days after the onset of his illness. A thoracic tap done three days later yielded cloudy brownish fluid in which type VII pneumococci were present. He was at first treated by closed intercostal drainage and irrigations with 1:3,300 azochloramide with a tertigol penetrant (sodium tetradecyl sulfate) but a rib resection was finally performed, and he recovered. He had received 23 Gm of sulfadiazine in addition to 210,000 units of rabbit serum.

There were 6 patients with sterile pleural effusions in the sulfadiazine-treated group, with 2 deaths and 7 in the other group, without fatality. In the former group 3 patients had fluid in the pleural spaces on admission to the hospital. In the latter group signs of fluid developed in all but 2 patients during therapy. One of the patients who succumbed (patient 20) was a 65 year old Negress admitted on the second day of her illness with a diagnosis of pneumonia of the lower lobe of the right lung and pleural effusion. Pneumococcus type III was found in her sputum. Thoracentesis the next day yielded sterile serous fluid containing 9,000 white blood cells per cubic millimeter predominantly mononuclear cells. Two days after the third thoracic tap (fifteenth day of hospitalization) a tension pneumothorax developed which necessitated decompression by underwater drainage. The patient seemed to be improving but died suddenly three days later, markedly dyspneic. An electrocardiogram taken three days after admission to the hospital showed evidence of myocardial damage. She received a total of 28 Gm of sulfadiazine and on two occasions its concentration in the blood was 8.9 and 13.6 mg per hundred cubic centimeters. No postmortem examination was done.

The other fatality occurred in a 50 year old white man (patient 4) admitted on the fifth day of his illness. He died thirty-two hours later. He had fluid in his right pleural cavity from the base almost to the apex with a moderate shift of the mediastinum to the opposite side. Three blood cultures were positive for Pneumococcus type VIII. The day after admission 100 cc of serosanguineous fluid was withdrawn from the chest. The organism was found in the thoracic fluid on culture, but it probably was present in the blood which was mixed with the fluid. The patient received only 4 Gm of the drug, when he died in a comatose state and in pulmonary edema. Antibody studies were not done.

An uncommon complication was encountered in a 16 year old boy (patient 15, fig. 2), who gave a three day history of abdominal pain and vomiting. Signs of consolidation were present over the upper lobe of the right lung. His sputum and blood contained pneumococcus type V. He received three courses of therapy with sulfadiazine, totaling 77 Gm, and 520,000 U S P units of rabbit anti-pneumococcus. His response to therapy was poor. A pericardial friction rub was heard sixteen days after admission. Roentgenograms revealed progressive enlargement of the cardiac shadow. Pericardial taps yielded small amounts of hemorrhagic fluid, which was sterile on culture. His blood contained both Pneumococcus type V and its capsular carbohydrate. He made a slow but apparently complete recovery and was discharged after seventy-six days in the hospital. His hematologic response will be presented elsewhere in this paper.





*Associated Diseases*—The incidence of associated or concurrent disease was 18.5 per cent (in 43 patients of 232) in the sulfadiazine-treated group and 13 per cent (in 9 patients of 70) in the other group. In the former group there were 18 patients with heart disease, 9 of whom died; they have been previously discussed. Of the patients who recovered, only 2 were in congestive failure (mild) and 2 others gave histories of previous hospitalizations for decompensation. In 1 of the patients, admitted in heart failure, lobar pneumonia developed twenty-five days after admission to the hospital; he recovered. He was readmitted nine months later in congestive cardiac failure and died.

In the group given both sulfadiazine and serum there were 3 patients with cardiac disease, 1 of whom died. She gave a history of heart disease of one year's duration and did not have cardiac failure when admitted to the hospital. Her death was attributable to her severe pulmonary infection due to *Pneumococcus* type III. In addition to bacteremia, her blood contained capsular carbohydrate in abundance up to the time of her death. One of the patients who recovered had signs of decompensation on admission. He had rheumatic heart disease with auricular fibrillation; his response to digitalis and diuretics was good.

In the entire series there were 10 patients with diabetes mellitus, all of whom recovered. Three had mild acidosis. Of the 10, 7 knew they had had diabetes for varying lengths of time, and in 3 patients the disease was discovered during routine urinalysis and chemical studies of the blood. Only 3 had moderately severe diabetes; the remainder had a mild form of the disease. For most of the patients the presence of the diabetes did not materially increase the length of their stay in the hospital.

There were 6 patients with pulmonary diseases other than pneumonia, of whom 2 had tuberculosis (fibrotic), 2 had asthma and 1 each had bronchitis and a pulmonary abscess; the last-named patient died. One patient had an advanced carcinoma of the esophagus, and another had carcinoma of the stomach; both died. Two patients had benign nephrosclerosis; hydronephrosis on the right side was encountered in another. Two patients were pregnant, 1 of whom was at term and was delivered of a normal child. Two patients had lymphogranuloma venereum with rectal strictures; both died. Multiple duodenal ulcers were also encountered post mortem in 1 of these patients. Of the 2 patients who had delirium tremens, 1 died. One patient each had fractured ribs, peptic ulcer, severe scleroderma and bacteremia associated with paratyphoid fever.

*Toxic Manifestations*—In the entire series there were 23 patients who experienced nausea or vomiting or both; this is an incidence of 7.6 per cent. One patient complained of nausea only, and another vomited without experiencing nausea. Of the remaining 21 patients, 7 showed these reactions on only one occasion. The complaints of all but 3 patients were relatively mild. In no instance in this series were these reactions severe enough to warrant discontinuing drug therapy. In most patients the nausea and vomiting appeared after the first few doses of sulfadiazine and subsided, though therapy was continued. Those who vomited prior to receiving the drug were not included. In the entire series no gross or microscopic hematuria was encountered, though crystals were frequently found in the urine. Nitrogen retention (creatinine 2.5 mg. per hundred cubic centimeters and urea nitrogen 95 mg. per hundred cubic centimeters) developed in 1 patient during therapy. Urea clearance several days later was 75 per cent of normal. Without special therapy the renal function and the chemical aspects of the blood returned to normal in several days. One patient experienced a severe chill and a sharp drop in temperature to normal, as well as marked clinical improvement,

after receiving about 1 Gm of sodium sulfadiazine by continuous infusion. This reaction was probably not due to the drug, since administration of 5 Gm of sodium sulfadiazine in 1 per cent concentration in solution of sodium chloride some time later to the same patient failed to produce it. We have not observed any mental reactions (in this series) definitely attributable to the drug. We observed neither leukopenia nor anemia as a result of the drug therapy. There were, however, 3 patients who had a low total white cell count but were given sulfadiazine because it was felt that the leukopenia was due to the severity of the infection and that intensive immediate therapy was indicated. One patient with type VII pneumococcus pneumonia had a total white cell count of 2,950, with 33 per cent segmented and 53 per cent nonsegmented neutrophils. A smear of his bone marrow showed myelocytic activity. He received a total of 47 Gm of sulfadiazine. His white cell count rose to 11,000 during therapy. A second patient had lobar pneumonia caused by a type II pneumococcus, bacteremia and pleural effusion. His blood showed 6,000 white cells, with 40 per cent segmented and 12 per cent nonsegmented neutrophils. Because his bone marrow showed marked myelocytic hyperplasia, he was given sulfadiazine. In addition to 33 Gm of the drug, he received 200,000 U S P units of rabbit antipneumococcus serum. On the fifth day of therapy his white cell count rose to 27,500, and before discharge it was 11,425. The third patient was a 16 year old boy (patient 15) with lobar pneumonia caused by a type V pneumococcus and pericarditis (fig 2). His initial white cell count was 1,900, with 8 per cent mature polymorphonuclears and 84 per cent nonsegmented neutrophils. He received three courses of sulfadiazine therapy totaling 77 Gm, as well as 520,000 U S P units of rabbit antipneumococcus serum. Three days after therapy was started his white cells numbered 8,450, of which 70 per cent were mature neutrophils. Within a week his white cell count had risen to 20,900. Sternal puncture disclosed an active bone marrow. It should be noted that all 3 patients, though having a low total white cell count, had a high percentage of granulocytes, with a marked shift to the left. They also had active bone marrow. These findings are evidence of severe infection and are indications for intensive chemotherapy. All 3 patients recovered.

One patient of the entire 302 considered in this report had a rash that was probably due to sulfadiazine. She was a 42 year old Negress with a type XXIV pneumococcus pneumonia who had received 37 Gm of the drug. Seven days after therapy had been stopped an erythematous pruritic rash developed over her face and chest accompanied by a rise in temperature which ranged between 101 and 103.2 F for thirty-six hours. She had received no other medication that might have been responsible for this phenomenon. Although the rash and fever occurred a week after the last dose of the drug had been given, it was probably a delayed toxic manifestation.

#### COMMENT

In our group of patients with pneumonia for whom pneumococci could be typed the mortality of those treated with sulfadiazine alone is about the same as that reported by other investigators<sup>10</sup> for similar series of patients, although it is con-

10 (a) Flippin, H. F., Rose, S. B., Schwartz, L., and Domm, A. H. Sulfadiazine and Sulfathiazole in the Treatment of Pneumococcic Pneumonia. A Progress Report on Two Hundred Cases, *Am J M Sc* **201** 585, 1941. (b) Finland, M., Strauss, E., and Peterson, O. L. Sulfadiazine. Therapeutic Evaluation and Toxic Effects on Four Hundred and Forty-Six Patients, *J A M A* **116** 2641 (June 14) 1941. (c) Dowling, H. F., Hartman, C. R., Sugar, S. J., and Feldman, H. A. The Treatment of Pneumococcic Pneumonia with Sulfadiazine, *ibid* **117** 824 (Sept 6) 1941. (d) Flippin, H. F., Rose, S. B., Schwartz, L., and Domm, A. H. Treatment of Pneumococcic Pneumonia with Sulfadiazine and Sodium Sulfadiazine, *War Med* **2** 284 (March) 1942.

siderably higher than that reported by Billings and Wood<sup>11</sup> (13 per cent). The incidence of bacteremia in our group was somewhat less than in the first four of the five series referred to and greater than in the last. The incidence of patients over 40 years of age was about the same as that reported by the other authors. In our group 68 per cent of the patients were admitted to the hospital late in the course of illness, whereas only 39 per cent of the series reported by Flippin and associates,<sup>10a</sup> 44 per cent of the series reported by Dowling and his co-workers<sup>10c</sup> and 33 per cent of the series reported by Flippin and his associates<sup>10d</sup> in a subsequent paper fell into that category. Because of the possibility that the delay of treatment for some hours to allow for specific typing of the infecting pneumococcus may have influenced our mortality rate, we have since July 1941 been instituting chemotherapy as soon as a diagnosis of pneumonia is made. Before therapy is begun, specimens of sputum and blood are obtained for study. In those cases in which typing is successful type-specific serum is then given to alternate patients unless they have already responded to chemotherapy.

It is the practice of our service to discontinue chemotherapy entirely after the temperature and the pulse have fallen to normal and remained so for eighteen to twenty-four hours. In this series it was found that the temperatures of 83 per cent of the patients treated with sulfadiazine alone remained normal (below 100 F) after therapy was discontinued. In the remaining 17 per cent, who had a secondary rise in temperature, the febrile episodes were usually relatively mild and of short duration. Our method of terminating chemotherapy is more economical and probably results in a lessened incidence of toxic reactions than does the method of tapering.

In our present series, as well as in those of the other investigators, the mortality among patients who received type-specific serum in addition to sulfadiazine was slightly higher than among those who were treated with the drug alone. This greater mortality is accounted for by the deliberate choice of the more severely ill patients for combination therapy and by the elimination from combined therapy of the least severely ill patients by their prompt response to chemotherapy alone. In our series 20 per cent of the patients treated with serum and sulfadiazine were selected because of bacteremia, detection of specific soluble substance in the blood or failure to respond to sulfadiazine alone. The remainder were unselected, and alternate patients were given serum. Comparison of the two groups reveals that the incidence of blood cultures positive for pneumococci was twice as great in the group undergoing combination therapy as in the other. The presence of circulating capsular carbohydrate was about three times as frequent in the former group as in the latter. (This difference approaches statistical significance— $R D E = 18$ .) There was a greater proportion of patients with infection due to type III pneumococci, which has a high mortality rate, in the group given both sulfadiazine and serum. The distribution as to age and day of illness on which therapy was begun was approximately the same in both groups. On the other hand, there were more deaths within twenty-four hours after admission in the sulfadiazine-treated group. The patients who received both therapeutic agents were undoubtedly more severely ill. The slightly higher mortality is explained by this definite difference in severity; the mortality in the group given both agents might have been higher if serum had not been given. We agree with other investigators<sup>12</sup> that there are a number of severely ill patients for whom serum is life saving. Final judgment as to the absolute value of this therapeutic agent must await results obtained from studies

11 Billings, F T, Jr, and Wood, W B, Jr. Studies on Sulfadiazine. The Use of Sulfadiazine in the Treatment of Pneumococcal Pneumonia, *Bull. Johns Hopkins Hosp.* 69:314, 1941.

12 Footnote 10a, b and c.

of comparable patients. All the factors which are known to influence prognosis, such as age, duration of illness, bacteremia, detection of capsular polysaccharide and concurrent disease, must be taken into consideration.

The toxic manifestations associated with sulfadiazine were both less frequent and less severe than those encountered with sulfapyridine. Rarely was it found necessary to discontinue its administration. The more serious reactions, such as anemia, obstruction of the urinary tract<sup>13</sup> and granulocytopenia, were not observed in this series.

#### SUMMARY AND CONCLUSIONS

Two hundred and thirty-two patients with pneumococcic pneumonia were treated with sulfadiazine, and 70 received type-specific rabbit antipneumococcus serum in addition to the drug.

The gross mortality was 13.4 per cent in the former group and 14.3 per cent in the latter.

Those patients over 40 years of age treated late in the course of their illness were most numerous in both groups and had the highest mortality.

Fifty-eight and seven-tenths per cent of the drug-treated patients and 43 per cent of those in the other group had normal temperatures within forty-eight hours after the institution of therapy.

In the sulfadiazine-treated group two thirds of the patients who recovered received between 10 and 24 Gm. of the drug, two thirds of the patients had blood concentrations of free drug ranging from 5 to 10 mg. per hundred cubic centimeters.

Chemotherapy was discontinued after the temperature had been normal for eighteen to twenty-four hours. The temperatures of 83 per cent of the patients in the sulfadiazine-treated group who recovered remained normal after chemotherapy had been stopped. The remaining 17 per cent had a rise in temperature which was mild and of short duration in most instances.

Sulfadiazine is as effective as sulfapyridine in the treatment of pneumococcic pneumonias.

The mortality among patients who received both serum and sulfadiazine was slightly higher than that among the sulfadiazine-treated patients, but the former group was composed of more severely ill patients.

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13 Since the preparation of this paper, numerous reports have appeared concerning renal damage—transitory and fatal—caused by sulfadiazine. We have since seen patients with hematuria and with oliguria, 1 of whom, severely stricken, died. This problem is under investigation in our service.

# ACUTE BRUCELLOSIS

## CLINICAL, BACTERIOLOGIC AND SEROLOGIC STUDIES OF THREE PATIENTS

BOWMAN WISE, M D

DURHAM, N C

Perusal of the large number of case reports of undulant fever contained in the literature is unsatisfactory not only because of frequent justifiable doubt as to the correctness of the diagnosis but because of the paucity of bacteriologic and serologic studies. Recently 3 patients suffering from undulant fever have afforded an excellent opportunity for study of the persistence of bacteremia and the behavior of demonstrable serum antibodies for *Brucella* throughout the course of the illness. The techniques used for blood cultures and for the serologic tests have been described elsewhere<sup>1</sup>. All 3 patients came under observation during the first month of illness, and all received treatment with sulfonamide drugs, the results of which will be discussed.

### REPORT OF CASES

CASE 1—C M, a 35 year old white man, a salesman, entered the hospital on Jan 13 1941, complaining of chills and fever of three weeks' duration. The familial, marital and past histories were irrelevant. He had frequently drunk unpasteurized milk.

The patient's illness began about Dec 15, 1940 with malaise, fever, headache and mild pain in the upper part of the abdomen. At the onset he remained in bed for five days having daily chills and fever, but he felt sufficiently well to return to work on December 20. Three days later he again had fever and chills, these lasted three days and were followed by a relatively symptom-free interval of three days, after which daily fever, with the temperature reaching 40 C (104 F), and irregular chills became established. During the first two weeks of his illness he was given quinine, without improvement. On Jan 6, 1941 he was admitted to another hospital. Physical examination revealed his liver to be palpable 2 cm below the costal margin, splenic dullness to percussion was increased, but the spleen was not palpable. The hemoglobin content was 98 per cent and the white blood cell count 6,500, with polymorphonuclear leukocytes 42 per cent and small lymphocytes 58 per cent. Blood smears were positive for tertian malaria, and he was given quinine sulfate in doses up to 2 Gm daily, without improvement. His temperature rose daily to 38 and 40 C (100.4 to 104 F). Repeated blood smears were negative for malarial parasites. Blood serum sent to the state laboratory was reported to give a positive agglutination reaction for undulant fever, and the patient was referred to Duke Hospital.

On admission the temperature was 38.7 C (101.7 F), the pulse rate 94, the respiratory rate 18 and the blood pressure 110 systolic and 60 diastolic. The patient appeared acutely ill. The pharynx was reddened. The heart and lungs were not remarkable. There was no abdominal tenderness. The edge of the liver was barely palpable, the spleen was felt 3 cm below the costal margin. The remainder of the physical examination revealed nothing remarkable.

The Wassermann and Kahn reactions of the blood were negative. The hemoglobin content was 95 per cent, the red blood cells numbered 4,500,000 and the white blood cells 8,000, with polymorphonuclear leukocytes 51 per cent (stab forms 23 per cent), eosinophils 0, basophils 0, large lymphocytes 0, small lymphocytes 43 per cent, early lymphocytes 4 per cent and monocytes 2 per cent. The urine and stools were normal. *Brucella suis* was isolated from the blood, and the serum agglutinated brucella organisms through titers to 1:2,560. Subsequent cultural and serologic studies are summarized in chart 1.

During the first three days of the patient's stay in the hospital his temperature varied between 38.5 and 40.4 C (101.3 and 104.7 F). On the third day the administration of sulfathiazole was started in daily doses of 6 Gm. There was a gradual fall in temperature during the first week of drug therapy, at which time the patient complained for several days of severe pain in his heels, without objective findings. At the time of discharge from the hospital, on February 1, the patient was afebrile and symptom free, and the spleen was no longer palpable.

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The patient returned for examination on February 25 and on March 25, having felt well during the intervals. Physical examination showed nothing remarkable. Cultures of blood taken on these visits were positive for *Br suis*. He returned on April 25, complaining of dull aching pain in the lower thoracic portion of the spine of five days' duration. This pain was relieved by local application of heat and was greatly increased by attempts to lift anything. Examination revealed no tenderness over the vertebral spinous processes and no pain on motion of the spine. Roentgenograms of the spine were normal. Admission to the hospital was advised but refused.

The patient returned home and experienced marked increase in the pain in his back, requiring morphine for relief. A slight daily elevation of temperature was noted. He reentered the hospital on May 2.

The temperature was 38.5 C (101.3 F), pulse rate 84, respiratory rate 16 and blood pressure 128 systolic and 70 diastolic. The patient appeared ill and in great pain. There were point tenderness over the twelfth thoracic vertebra and severe pain on motion of the spine and lower parts of the legs. The results of the remainder of the physical examination were not remarkable.

The hemoglobin content was 114 per cent, the red blood cells numbered 5,520,000 and the white blood cells 4,850, with polymorphonuclear leukocytes 54 per cent, eosinophils 0, basophils 0, large lymphocytes 10 per cent, small lymphocytes 28 per cent, early lymphocytes 2 per cent.

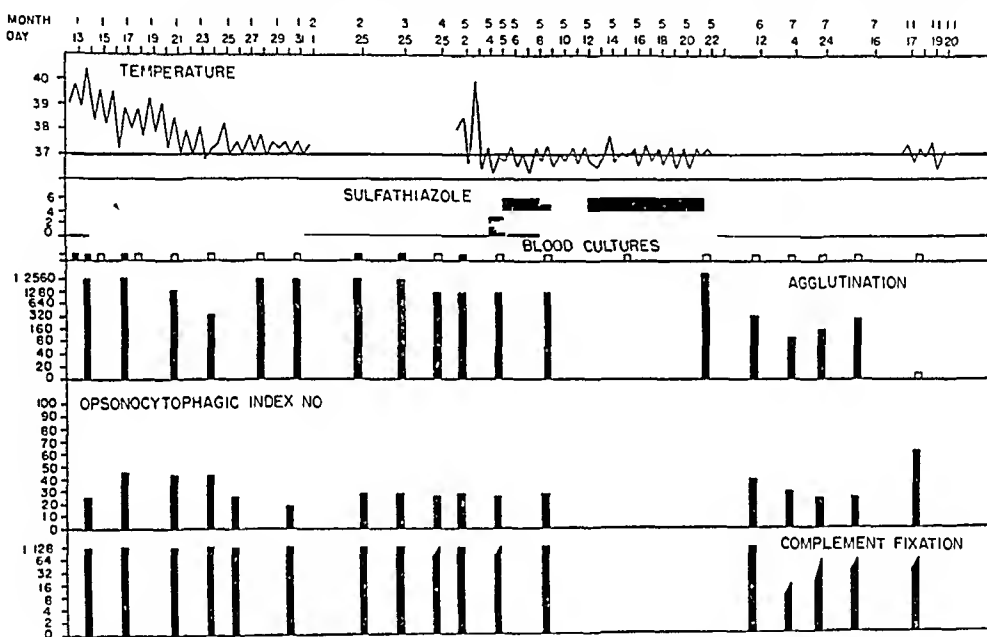


Chart 1 (case 1) —Bacteriologic and serologic observations. The filled-in spaces indicate positive and the blank spaces negative results. The sulfathiazole is expressed in grams.

and monocytes 6 per cent. The urine and stools were normal. *Br suis* was isolated from blood taken on the day of admission. Other bacteriologic and serologic observations are given in chart 1. Roentgenograms of the spine showed no definite changes.

The patient's temperature fell promptly to a normal level, and after application of a plaster body jacket the pain in his back gradually improved. Administration of sulfathiazole (2-[para-aminobenzenesulfonamido]-thiazole) in daily doses of 6 Gm was started four days after admission and continued throughout his stay in the hospital. He was greatly improved at the time of discharge, on May 23.

The patient was seen at intervals during the succeeding three months and complained only of occasional pain in the back. Repeated roentgenograms of his spine failed to show any definite lesion. Blood cultures were negative. He returned to the hospital on November 17, complaining of a "cold" of one week's duration. Chilliness and fever, with a temperature to 38.8 C (101.8 F), had been noted five days before admission. Although all symptoms of rhinitis and pharyngitis had abated by the time of his visit, he was admitted to the hospital for observation.

The temperature was 37.2 C (100 F), pulse rate 80, respiratory rate 20 and blood pressure 130 systolic and 70 diastolic. The results of physical examination were not remarkable. The hemoglobin content was 109 per cent, the red blood cells numbered 5,150,000 and the white blood cells 5,880, with polymorphonuclear leukocytes 38 per cent (stab forms 8 per cent), eosinophils 1 per cent, basophils 0, large lymphocytes 34 per cent, small lympho-



The Wassermann and Kahn reactions of the blood were negative, the hemoglobin content of the blood was 78 per cent, the red blood cells numbered 4,620,000 and the white blood cells 5,800, with polymorphonuclear leukocytes 55 per cent (stab forms 6 per cent and juvenile cells 3 per cent), eosinophils 1 per cent, basophils 0, large lymphocytes 19 per cent, small lymphocytes 28 per cent and monocytes 1 per cent. Examinations and cultures of the urine and stools gave negative results. Br suis was isolated from the blood, and serum agglutinins for brucella were present in a titer of 1:2,560. Subsequent bacteriologic and serologic observations are given in chart 2.

On the patient's admission to the hospital his abdominal pain promptly disappeared. On the fourth day in the hospital the temperature, which had risen daily to 39.5 C (103.1 F), fell to 38.5 C (101.3 F) and it did not rise above 37.9 C (100.2 F) during the succeeding week, for which reason sulfonamide drugs were not given. However, the temperature again rose daily to 40 C (104 F), so the administration of sulfathiazole was started in daily doses of 6 Gm. During the subsequent week there was a gradual fall of the temperature to normal. The daily dose of sulfathiazole was decreased to 5 Gm during the week preceding discharge. At the time of discharge, on April 21, the patient was entirely afebrile and symptom free, but his spleen was still palpable. A culture of blood taken on this day was positive for Br suis.

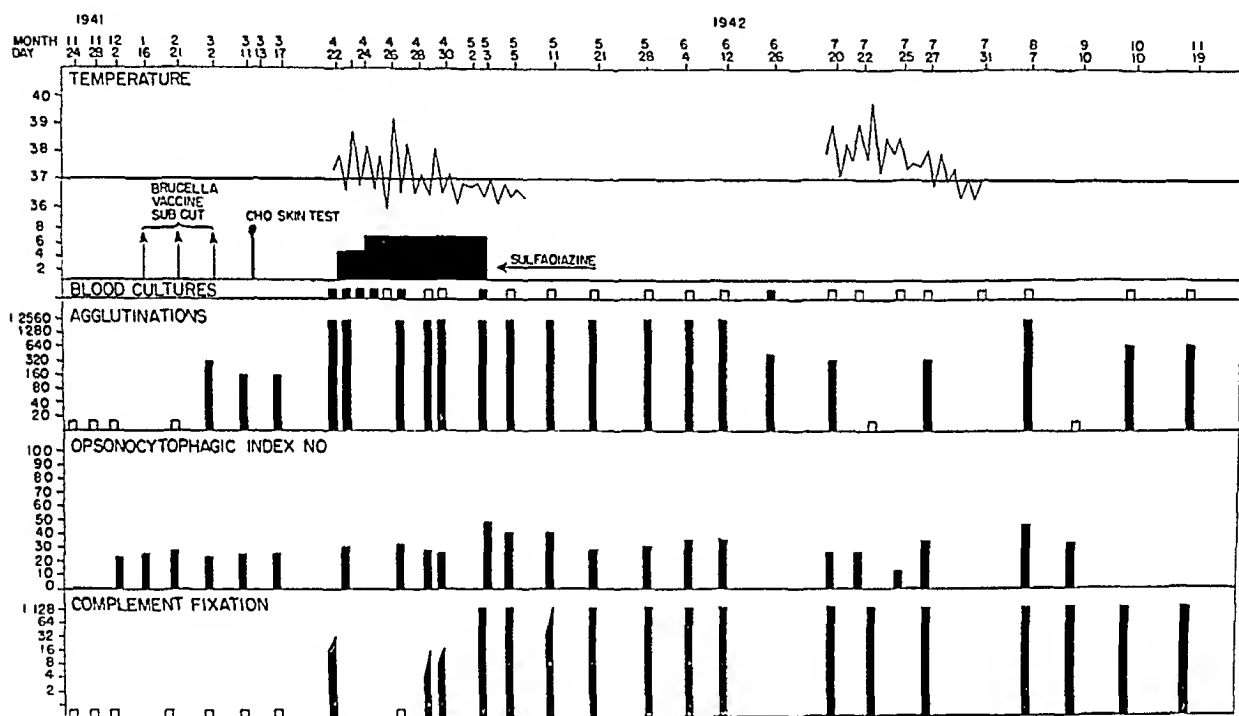


Chart 3 (case 3) —Bacteriologic and serologic observations. The filled-in spaces indicate positive and the blank spaces negative results. The sulfathiazole is expressed in grams.

He returned for examination on May 12, saying that he felt perfectly well and that he had gained 13 pounds (5.9 Kg). The results of physical examination were entirely negative, the spleen being no longer palpable. Cultures of blood taken on this and subsequent visits were negative. He returned again on June 9, having continued to be in excellent health and having gained an additional 10 pounds (4.5 Kg). He was last seen on September 8, at which time he was discharged from observation.

CASE 3—D S, a 25 year old man, a technician employed in the brucellosis laboratory, was admitted to the hospital on April 22, 1942, complaining of general malaise. The past history was noncontributory. In March 1941 he was given three subcutaneous injections of a brucella vaccine at weekly intervals.

At the time of admission his temperature was 37.2 C (99 F), pulse rate 92, respiratory rate 20 and blood pressure 120 systolic and 70 diastolic. There was slight enlargement of the superficial lymph nodes, but the remainder of the examination gave negative results.

The Kahn and Kline reactions were negative. The hemoglobin content was 103 per cent, the red blood cells numbered 5,270,000 and the white blood cells 4,800 with polymorphonuclear leukocytes 70 per cent (stab forms 6 per cent), eosinophils 0, basophils 0, large lymphocytes 1 per cent, small lymphocytes 24 per cent and monocytes 5 per cent. The urine was normal. Serum agglutinins and complement-fixing antibodies for Brucella were present in high titers,



and Br suis was isolated from the blood taken on admission. Subsequent bacteriologic and serologic observations are given in chart 3.

The patient was given sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) in daily doses of 6 Gm. His temperature gradually fell to normal, and he was discharged from the hospital on May 6, 1942. He was followed closely and, except for having an infection of the upper respiratory tract, remained well until July 15, when malaise again developed with arthralgia and fever. A culture of blood taken on June 26 was positive for Br suis. He was readmitted to the hospital on July 20.

On admission his temperature was 38.2 C (100.8 F), pulse rate 100 and respiratory rate 24. The results of physical examination were not remarkable. The hemoglobin content was 84 per cent, the red blood cells numbered 4,260,000 and the white blood cells 6,900 with polymorphonuclear leukocytes 42 per cent (stab forms 6 per cent), eosinophils 0, basophils 0, large lymphocytes 0, small lymphocytes 44 per cent, early lymphocytes 1 per cent and monocytes 13 per cent. The urine was normal. A roentgenogram of the chest was normal. Further bacteriologic and serologic observations are given in chart 3.

The patient's treatment was entirely symptomatic. His fever gradually subsided, and he was discharged from the hospital on July 31. Since this time he has been followed closely and has remained well.

#### COMMENT

*1 Clinical and Laboratory Diagnosis*—The clinically suspected diagnosis of undulant fever requires substantiation by isolation of brucella organisms from the patient's blood or demonstration of brucella agglutinins in high titer in the patient's serum. Although the 3 patients described here had serum agglutinins in titers of 1:2560 or higher, as well as Br suis in the blood at the time they came under observation, agglutinins may not be demonstrable for weeks after the onset of illness. Demonstrable complement-fixing antibodies in the serum usually parallel agglutinins in time of appearance, but, as has been stated elsewhere,<sup>1c</sup> the complement fixation test has no real advantage over the more easily performed agglutination test for the diagnosis of brucellosis. Determination of the opsonocytophagic index has been found to be of no value for diagnosis.

According to our experience the clinical diagnosis requires differentiation of the condition from all fevers of undetermined origin, but brucellosis has been most frequently confused with typhoid fever and infectious mononucleosis. Although patients suffering from brucellosis rarely appear as ill as those suffering from typhoid fever, laboratory tests are necessary to establish the correct diagnosis. Significant enlargement of the superficial lymph nodes in brucellosis, to which Bloomfield has recently called attention,<sup>2</sup> may lead to confusion with infectious mononucleosis. Furthermore, the differential white cell count of patients suffering from acute brucellosis frequently reveals abnormal lymphocytes suggestive of the early stage of infectious mononucleosis.

*2 Fever, Bacteremia and Duration of Illness*—The 3 patients discussed here were febrile at the time they came under observation, and blood cultures were positive for Br suis. Febrile episodes lasted usually seven to ten days. The well known undulating type of fever in this disease is illustrated in chart 2 (case 2). The duration of the illness varied. Recovery from the initial episode of fever was apparently complete, and in the intervals between febrile episodes the patients were symptom free, despite the fact that bacteremia was demonstrated by recovery

1 (a) Wise, B., and Kerby, G. P. Cultivation of Brucella from the Blood, to be published. (b) Wise, B. An Evaluation of the Brucella Opsonocytophagic Test, *Am J M Sc* **200** 520-523 (Oct.) 1940. (c) Jersild, M. A Cytophagic Reaction Employed in the Diagnosis of Brucella Infection, *J Infect Dis* **68** 16-19 (Jan.) 1941. (d) Foshay, L., and LeBlanc, T. J. The Derivation of an Index Number for the Opsonocytophagic Test, *J Lab & Clin Med* **22** 1297-1300 (Sept.) 1937. (e) Wise, B., and Craig, H. W. The Brucella Complement-Fixation Reaction, *J Infect Dis* **70** 147-151 (March-April) 1942.

2 Bloomfield, A. L. Enlargement of the Superficial Lymph Nodes in Brucella Infection, *Am Rev Tuberc* **45** 741-750 (June) 1942.

of the organism from the blood. It is not generally recognized that positive blood cultures may be obtained long after complete recovery from the acute illness or even in the absence of a frank history of illness.<sup>3</sup> In cases 1 and 3 recurrence of bacteremia, shown by positive blood cultures, preceded recurrence of fever, but bacteremia without any return of fever or symptoms occurred in case 2. Such possibilities should be kept in mind in all cases of brucellosis and should serve as a caution against interpretation of a single positive blood culture as indicating clinical disease.

**3 Sulfonamide Therapy**—In a review of the use of sulfonamide drugs in the treatment of undulant fever, Blumgart and Gilligan<sup>4</sup> in 1939 concluded that sulfanilamide is a valuable therapeutic agent. They stated "The findings, following sulfanilamide treatment, of diminished agglutination titers and of negative blood cultures in cases which had shown positive cultures before treatment, bear further evidence that the infection is controlled." Recent in vitro experiments have shown sulfathiazole and sulfadiazine to have an almost equal bacteriostatic action on *B. suis* and one considerably more pronounced than that of sulfanilamide.<sup>5</sup> In the 3 cases reported sulfathiazole or sulfadiazine was given with little or no apparent benefit. Possibly the drugs had some effect in reducing the bacteremia, but subsequent positive blood cultures were obtained in all cases, even as early as several days after administration of the drug was discontinued. It seems likely that the number of positive blood cultures obtained in cases of undulant fever, both during and after the febrile illness, depends primarily on the number of cultures made and also on the cultural technic employed. It is of particular interest to compare the persistence of bacteremia in the case reported by Keefer<sup>3a</sup> in 1924, in which no specific treatment was given with that in the 3 instances reported here. Regardless of whether sulfonamide drugs are considered to have some beneficial effect in sterilizing the blood during the initial febrile episode, or possibly shortening the course of the illness, the use of these drugs has failed to prevent relapse.

**4 Serologic Reactions Persistence of Serum Antibodies**—No significant changes in titers of brucella agglutinin or complement-fixing antibodies were observed after sulfonamide therapy in the cases reported. When agglutination and complement fixation tests are carried out at frequent intervals, considerable variations in titers may be observed over a period of days regardless of whether or not chemotherapy is used. A relatively prompt disappearance of demonstrable serum agglutinins usually follows complete recovery, but complement-fixing antibodies, as is well known, may persist for months. The results of determinations of the opsonocytophagic index have been so variable as to preclude discussion. This experience is in complete agreement with that of Castaneda, Tovar Mancera and Velez.<sup>6</sup>

3 (a) Keefer, C. S. Report of a Case of Malta Fever Originating in Baltimore, Maryland, *Bull. Johns Hopkins Hosp.* **35** 6-14 (Jan.) 1924. (b) Shaw, E. A. II. The Ambulatory Type of Case in Mediterranean or Malta Fever, *Mediterranean Fever Reports*, London, 1907, pt. 4, pp. 8-15.

4 Blumgart, H. L., and Gilligan, D. R. The Treatment of Undulant Fever with Sulfanilamide and Related Compounds, *M. Clin. North America* **23** 1193-1203 (Sept.) 1939.

5 (a) Kempner, W., Wise, B., and Schlayer, C. Manometric Determination of the Effects of Various Sulfanilamide Compounds on *Brucella melitensis*, *Am. J. M. Sc.* **200** 484-492 (Oct.) 1940. (b) Wise, B. In Vitro Studies of Sulfonamide Action on Organisms of the *Brucella* Group and the Counteracting Effect of Para-Aminobenzoic Acid, *J. Pharmacol. & Exper. Therap.* **76** 156-160 (Oct.) 1942.

6 Castaneda, M. R., Tovar Mancera, R., and Velez, R. Studies on Brucellosis in Mexico. Comparative Study of Various Diagnostic Tests and Classification of the Isolated Bacteria, *J. Infect. Dis.* **70** 97-102 (March-April) 1942.

5 *Complications and Sequelae*—Neither complications nor sequelae were observed in cases 2 and 3. Although osteitis, a fairly common complication of undulant fever,<sup>7</sup> was strongly suspected in case 1, no lesion was ever satisfactorily demonstrated by roentgenologic examination.

#### SUMMARY

1 The clinical histories and bacteriologic and serologic observations in 3 cases of undulant fever are presented and discussed.

2 Emphasis is placed on the persistence and recurrence of bacteremia, which may be detected in symptom-free intervals between febrile episodes as well as after complete recovery.

3 The behavior of demonstrable serum agglutinins and complement-fixing antibodies during and after the period of illness is illustrated.

4 It is noted that the therapeutic effect of sulfathiazole or sulfadiazine in these cases was not striking.

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<sup>7</sup> Bishop, W. A. Vertebral Lesions in Undulant Fever, *J. Bone & Joint Surg.* **21**: 665-763 (July) 1939.

# ALTERATIONS IN BIOLOGIC OXIDATION IN THYROTOXICOSIS

## I THIAMINE METABOLISM

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A great deal of evidence has accumulated to indicate that the thyroid gland is a part of an integrated system which regulates biologic oxidations. The nervous system, the pituitary gland and the cells and fluids of the body are other important entities in this system (chart 1). Disturbance in any one of these units may affect the functions of the others. For example, removal of the pituitary gland results in decreased function of the thyroid gland, the body cells and the nervous system. Removal of the thyroid leads to increased production of the thyrotropic hormone and to decreased activity of the body cells and the nervous system. Conversely, with thyrotoxicosis or the feeding of thyroid there is stimulation of the nervous system and the metabolism of the body cells. Alterations in biologic oxidations of the cells have been demonstrated to exert an effect on the segments of the system shown in chart 1, however, little consideration has been given to the concept that certain abnormalities in the functions of the body cells might lead to the development of thyrotoxicosis.

Webster and Chesney <sup>1</sup> have found that in rabbits fed a diet consisting chiefly of cabbage goiter of a hyperplastic type developed and the metabolic rate was lowered. However, within a few days after iodine was given to these goitrous animals, they exhibited signs of thyrotoxicity and a marked elevation of the metabolic rate. When iodine was given at the beginning of the cabbage diet it offered complete protection against the goitrogenic effects of cabbage <sup>2</sup>. Marine, Baumann, Spence and Cipra <sup>3</sup> demonstrated that a cabbage diet induces goiter because the cyanide it contains inhibits the consumption of oxygen. Rabbits fed methyl cyanide had the same type of goiter <sup>4</sup>. Moreover, the simultaneous administration of iodine tended to prevent the goitrogenic effects of the cyanide.

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<sup>1</sup> Fellow (Chile) of the Rockefeller Foundation 1941-1942. Dr Egana did not read this manuscript because of difficulties in getting it transported to Chile.

1 Webster, B, and Chesney, A M. Endemic Goiter in Rabbits. III Effect of Administration of Iodine, *Bull Johns Hopkins Hosp* **43** 291, 1928.

2 Webster, B, and Chesney, A M. Studies in the Etiology of Simple Goiter, *Am J Path* **6** 275, 1930.

3 Marine, D, Baumann, E J, Spence, A W, and Cipra, A. Further Studies on Etiology of Goiter with Particular Reference to the Action of Cyanides, *Proc Soc Exper Biol & Med* **29** 772, 1932.

4 Marine, D, Rosen, S H, and Cipra, A. Further Studies on the Exophthalmos in Rabbits Produced by Methyl Cyanide, *Proc Soc Exper Biol & Med* **30** 649, 1933.

Uotila<sup>5</sup> found that rats continuously exposed to cold had an increase in the thyrotropic function and marked hyperplasia of the thyroid cells. However, if the pituitary stalk was sectioned before the animal was subjected to the cold, such changes were not found. These observations emphasize the interrelation of the various segments of the system presented in chart 1.

Means, Hertz and Lerman<sup>6</sup> noted that hyperthyroidism developed in some patients while they were following a strenuous regimen for the reduction of weight. We have seen this phenomenon sufficiently often to suspect that certain dietary restrictions may lead to the development of thyrotoxicosis. It is of interest that various deficiencies of vitamins, as well as of other substances, have been said to promote the development of goiter. Spence<sup>7</sup> observed the development of simple goiter in 15 of 20 rats kept on a diet deficient in vitamins A, B, C and D. Sandberg and Holly<sup>8</sup> reported that in rabbits kept on a diet deficient in vitamin B<sub>1</sub>, hyperplasia of the thyroid developed but that administration of vitamin B<sub>1</sub> to these animals with goiter caused only slight change in the anatomic state of the gland. However, Fischer<sup>9</sup> found not only that vitamin B<sub>1</sub> plays a contributory part in the production of endemic goiter but that the feeding of this vitamin in unpolished

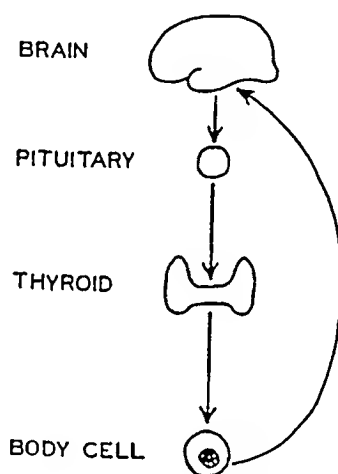


Chart 1—An integrative system concerned with biologic oxidations

rice produces the same histologic effect on the thyroid gland as the feeding of iodized salt. On the other hand, Carpenter and Sharpless<sup>10</sup> concluded that vitamin B deficiency alone does not affect the size, structure or iodine content of the thyroid gland of the rat.

Thus, one can see that the cellular oxidations have distinct influences on the thyroid gland, but further study is necessary to establish the precise nature and extent of these relationships.

5 Uotila, N. N. Role of Pituitary Stalk in Regulation of Thyrotropic and Thyroid Activity, *Proc Soc Exper Biol & Med* **41** 106, 1939.

6 Means, J. H., Hertz, S., and Lerman, J. Nutritional Factors in Graves' Disease, *Ann Int Med* **11** 429, 1937.

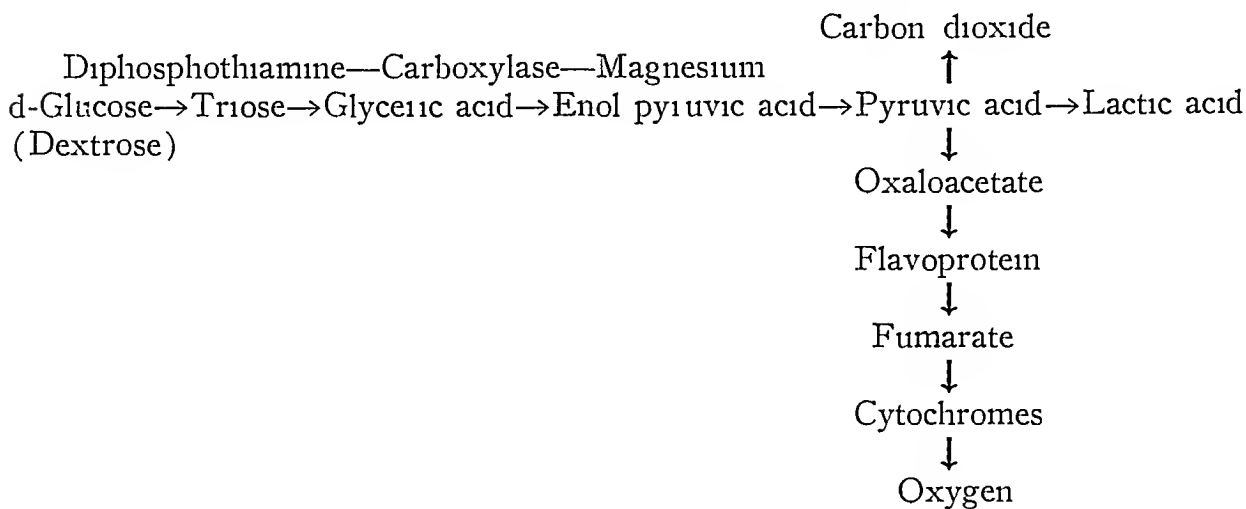
7 Spence, A. W. The Effect of Vitamin Deficiency on the Structure of the Thyroid and Thymus Glands, *Brit J Exper Path* **13** 157, 1932.

8 Sandberg, M., and Holly, O. M. On the Influence of Vitamin B and of Iodine on the Calcium and Phosphorus Metabolism of Rabbits with Hyperplastic Thyroids, *J Biol Chem* **99** 547, 1933.

9 Fischer, E. Production and Prevention of Goiter in Rat Experiments, *Nutrition Abstr & Rev* **3** 827, 1934.

10 Carpenter, M. D., and Sharpless, G. R. A Study of the Effect of Vitamin B and Iodine on the Weight, Iodine Content and Structure of the Thyroid Gland of the Rat, *J Nutrition* **13** 235, 1937.

At the Thoindike Memorial Laboratory we have been investigating in thyrotoxic patients the nature of the reactions of the various segments of the system of biologic oxidations, as presented by von Szent-Gyorgyi<sup>11</sup> The following outline shows some of the steps involved in the oxidation of dextrose



In this report we are concerned chiefly with the interrelationship of the thyroid and thiamine functions, particularly the effects of the former on the latter. First, however, we wish to mention some of the physiologic reactions of this vitamin.

The biologically active form of thiamine is cocarboxylase, or diphosphothiamine<sup>12</sup> Although the phosphorylation of thiamine occurs in all nucleated cells, the liver and kidneys are particularly active in this process. Almost all the thiamine found in the cells is in the phosphorylated form, whereas essentially all the thiamine in the plasma and urine is in the free form. Diphosphothiamine is primarily concerned with the decarboxylation of alpha ketonic acids, particularly pyruvic acid<sup>13</sup> In this capacity it is part of a protein-diphosphothiamine-magnesium compound in which the three components are present in the ratio of 1 : 1 : 5 or 1 : 1 : 7.

Diphosphothiamine is necessary for the transfer of phosphorus from phospho(enol)-pyruvic acid to adenylic acid, and, since pyruvate oxidations cause the storage of a considerable amount of energy as adenosine triphosphate, diphosphothiamine is indirectly involved in the synthesis of glycogen from d-glucose (dextrose). Diphosphothiamine is also necessary in the synthesis of fatty acids from carbohydrates, this action is probably secondary to its effect on pyruvate metabolism.

It may thus be noted that not only thyroid but diphosphothiamine is intimately concerned with cellular oxidation. Since it has been shown by Plimmer,<sup>14</sup> Cowgill and associates<sup>15</sup> and others<sup>16</sup> that the requirements of vitamin B are propor-

11 von Szent-Gyorgyi, A. On Oxidation, Fermentation, Vitamins, Health and Disease, Baltimore, Williams & Wilkins Company, 1939.

12 Ochoa, S. Cocarboxylase, in Symposium on Vitamins Held at the University of Chicago, Sept 15-17, 1941, Chicago, University of Chicago Press, 1942.

13 Banga, I., Ochoa, S., and Peters, R. A. Pyruvate Oxidation in Brain. VI. The Active Form of Vitamin B<sub>1</sub> and the Role of C<sub>1</sub> Dicarboxylic Acids, *Biochem J* **33** 1109, 1939.

14 Plimmer, R. H. A. Vitamins, *Brit M J* **1** 239, 1926. Plimmer, R. H. A., Rosedale, J. L., and Raymond, N. H. Experiments on Nutrition. VI. Balance of Food by Vitamin B, *Biochem J* **21** 913, 1927.

15 (a) Cowgill, G. R., and Palmieri, M. L. Studies in the Physiology of Vitamins. XXII. The Effect of Experimentally Induced Hyperthyroidism on the Vitamin B Requirement

nional to the amount of food metabolized, one might expect to find disturbances in thiamine metabolism in thyrotoxicosis. Many studies have been made of this subject with animals, but studies of patients are somewhat incomplete.

#### THYROTOXICOSIS OF ANIMALS

Rats maintained on a normal diet had essentially the same concentration of vitamin B<sub>1</sub> in the different tissues, although the concentration was slightly greater in the liver and heart<sup>17</sup>. When large quantities of the vitamin were fed, the concentration greatly increased in the liver and muscle but did not change appreciably in the other tissues. Animals kept on a diet deficient in vitamin B<sub>1</sub><sup>18</sup> for one month had no demonstrable thiamine in the tissues.

Rats given 12 Gm of normal diet and 100 mg of thyroid extract daily have been found to show a decrease in the thiamine content of the kidney and a marked decrease in that of the liver but a normal content in the spleen<sup>19</sup>. Animals maintained on the foregoing regimen and subsequently given by injection 500 micrograms of thiamine hydrochloride daily had a normal amount of thiamine in the spleen and muscle, a slightly raised content in the heart and a definite reduction in the liver and kidney when compared with normal rats receiving 500 micrograms of thiamine hydrochloride daily. The hyperthyroid rats receiving the thiamine eliminated the same amount of vitamin B<sub>1</sub> in the urine as did the normal rats given the same amount of thiamine. This suggests that the increased metabolism produced by the thyroid feeding did not increase the amount of vitamin B<sub>1</sub> destroyed by the body metabolism.

Peters and Rossiter<sup>20</sup> demonstrated that the cocarboxylase content of boiled tissue extracts from the hyperthyroid animals which they studied was intermediate in value between that from normal animals and that from animals showing symptoms of vitamin B<sub>1</sub> deficiency. The injection of thiamine hydrochloride increased the diphosphothiamine content of the tissues of both normal and hyperthyroid animals.

Dogs kept on a diet deficient in vitamin B and fed large doses of desiccated thyroid had anorexia and lost weight much sooner than dogs on the same diet without thyroid<sup>21</sup>. The administration of large doses of thiamine to these animals caused a marked increase in appetite and a gain in weight,<sup>22</sup> beginning within forty-eight hours<sup>23</sup>. Furthermore, dogs kept on a diet well supplemented with

of Pigeons, *Am J Physiol* **105** 146, 1933. (b) Himwich, H. E., Goldfarb, W., and Cowgill, G. R. Studies in the Physiology of Vitamins. XVII. The Effect of Thyroid Administration upon the Anorexia Characteristic of Lack of Undifferentiated Vitamin B, *ibid* **99** 689, 1932.

16 Hendricks, W. A. The Relation of Vitamin B Requirement to Metabolism, *ibid* **105** 678, 1933. Williams, R. R., and Spies, T. D. Vitamin B<sub>1</sub> and Its Use in Medicine, New York, The Macmillan Company, 1938, chap. 20.

17 Brodie, J. B., and MacLeod, F. L. Quantitative Experiments on the Occurrence of Vitamin B in Organs, *J Nutrition* **10** 179, 1935. Leong, P. C. Vitamin B<sub>1</sub> in the Animal Organism. I. The Maximum Storage of Vitamin B<sub>1</sub> in the Tissues of the Rat, *Biochem J* **31** 367, 1937.

18 The terms thiamine and vitamin B<sub>1</sub> are synonymous.

19 Drill, V. A. The Effect of Experimental Hyperthyroidism on the Vitamin B<sub>1</sub> Content of Some Rat Tissues, *Am J Physiol* **122** 486, 1938.

20 Peters, R. A., and Rossiter, R. J. Thyroid and Vitamin B<sub>1</sub>, *Biochem J* **33** 1140, 1939.

21 Cowgill, G. R., Rosenberg, H. A., and Rogoff, J. Studies in Physiology of Vitamins. Effect of Exercise on Time Required for Development of Anorexia Characteristic of Lack of Undifferentiated Vitamin B, *Am J Physiol* **98** 589, 1931.

22 Himwich, H. E., Goldfarb, W., and Cowgill, G. R. The Vitamin B Complex in Relation to Food Intake During Hyperthyroidism, *Proc Soc Exper Biol & Med* **28** 646, 1931.

23 Drill, V. A. The Calorie Intake and Weight Balance of Hyperthyroid Dogs in Relation to Vitamin B<sub>1</sub> and Yeast, *Am J Physiol* **132** 629, 1941.

vitamin B and fed thyroid did not tend to show anorexia or loss of weight. Yet, when very large doses of thyroid were given the animals lost weight and died<sup>24</sup> in spite of the fact that the tissue content of vitamin B<sub>1</sub> can be maintained at a normal level by the injection of large quantities of thiamine<sup>19</sup>. Some of these phenomena have been demonstrated in rats<sup>25</sup> and pigeons<sup>26</sup>. Sure and Buchanan,<sup>25</sup> working with rats, showed that a much better protection against the toxic effects of thyroxine was afforded by yeast than by thiamine alone. Furthermore, Drill and Sherwood<sup>27</sup> found that although vitamin B<sub>1</sub> stimulated the food intake of hyperthyroid rats, it did not promote gain in weight, under the conditions used, until a rich source of vitamin B complex was added to the diet.

Frazier and Friedman<sup>28</sup> found that the administration of thyroid to guinea pigs caused marked depletion of glycogen in the liver, the same diet without the thyroid permitted a gain in weight. The addition of iodine or dextrose to the diet did not increase the amount of glycogen in the liver. However, the studies of Drill<sup>29</sup> demonstrated that rats which received large quantities of vitamins B<sub>1</sub> and G plus thyroxine maintained a normal quantity of glycogen in the liver.

Abelin, Knuchel and Spichtin<sup>30</sup> reported that large amounts of casein, egg yolk or yeast in the diet of hyperthyroid animals lowered the basal metabolic rate, prevented the depletion of glycogen stores of the liver and muscles and prevented hepatic injury. Moreover, Drill and Hays<sup>31</sup> demonstrated that in dogs fed large quantities of thyroid, yeast afforded a marked protection to the hepatic function, as measured by the bromsulphalein test.

Buell, Strauss and Andrus<sup>32</sup> found that in the gastrocnemius muscles of severely thyroxinized animals the formation of lactic acid was inhibited, as evidenced by a lower initial value, slower rate of formation and earlier cessation of production than those of the normal animal. They also found a decreased glycogen content of the muscle but did not believe this was the cause of the decrease in production of lactic acid. They suggested that in the thyroxinized animal there may be a decreased capacity for the synthesis of glycogen from lactic acid.

In summary, studies with animals have shown that with the administration of large doses of thyroid there is a demand for an increased supply of thiamine, which if not supplied results in a depletion of the body stores of this vitamin leading to anorexia, loss of weight, decreased stores of glycogen in the muscles and liver and decreased hepatic function. These changes can be largely reversed or prevented by the concomitant administration of vitamin B<sub>1</sub> and the vitamin B complex.

24 Sure, B, and Smith, M. E. Hyperthyroidism and Nutrition. I. Vitamin B and Thyroxine, *J. Nutrition* **7** 547, 1934.

25 Sure, B, and Buchanan, K. S. Antithyrogenic Action of Crystalline Vitamin B, *J. Nutrition* **13** 513, 1937. Sure and Smith<sup>24</sup>.

26 (a) Cowgill, G. R., and Klotz, B. H. Determination of the Vitamin B Requirement of the Pigeon and Its Bearing on the Theory of Vitamin B Function, *Am. J. Physiol.* **81** 470, 1927. (b) Cowgill and Palmeri<sup>15a</sup>. Cowgill, Rosenberg and Rogoff<sup>21</sup>.

27 Drill, V. A., and Sherwood, C. R. The Effect of Vitamin B<sub>1</sub> and the Vitamin B<sub>2</sub> Complex on the Weight, Food Intake, and Estrus Cycle of Hyperthyroid Rats, *Am. J. Physiol.* **124** 683, 1938.

28 Frazier, W. D., and Friedman, H. Alterations in Liver Glycogen Following Thyroid, Iodine and Glucose Feedings, *Surg., Gynec. & Obst.* **60** 27, 1935.

29 Drill, V. A. The Effect of Yeast on the Liver Glycogen of White Rats During Hyperthyroidism, *J. Nutrition* **14** 355, 1937.

30 Abelin, I., Knuchel, M., and Spichtin, W. The Effect of Vitamins on the Course of Experimental Hyperthyroidism, *Biochem. Ztschr.* **228** 189, 1930.

31 Drill, V. A., and Hays, H. W. Hyperthyroidism and Liver Function in Relation to B Vitamins, *Proc. Soc. Exper. Biol. & Med.* **43** 450, 1940.

32 Buell, M. V., Strauss, M. B., and Andrus, E. C. Metabolic Changes Involving Phosphorus and Carbohydrate in the Autolyzing Gastrocnemius and Cardiac Muscles of Normal of Thyroxinized and of Adrenalectomized Animals. *J. Biol. Chem.* **98** 645, 1932.



## THYROTOXICOSIS OF PATIENTS

Frazier and Ravdin,<sup>33</sup> as well as Means,<sup>34</sup> have pointed out that in patients with exophthalmic goiter there are often symptoms suggesting thiamine deficiency. One of us (R H W) has been interested in this association for several years and has observed not infrequently the coexistence of hyperthyroidism, pellagra and ariboflavinosis. The tongue is sometimes fiery red and its papillae atrophic, hyperexia may be replaced by anorexia, and loss of weight becomes marked, achlorhydria, "dyspepsia," delayed emptying time of the stomach and diarrhea are fairly common. Tachycardia, cardiac dilatation, generalized edema, decrease in circulation time and vasomotor disturbances are also encountered. Decrease in strength and tolerance to exercise are almost always demonstrable.

Borison<sup>35</sup> found that the daily excretion of thiamine in the urine was below normal in most of a group of 8 thyrotoxic patients. He also found that the excretion of a test dose of thiamine was substandard in nearly each instance.

In order to secure further information as to the frequency of coexistence of thyrotoxicosis and thiamine deficiency, we determined the vitamin B content of the blood of 40 thyrotoxic subjects. The patients studied were scattered in seven hospitals in Boston and represented various social classes.<sup>36</sup> There was no selection

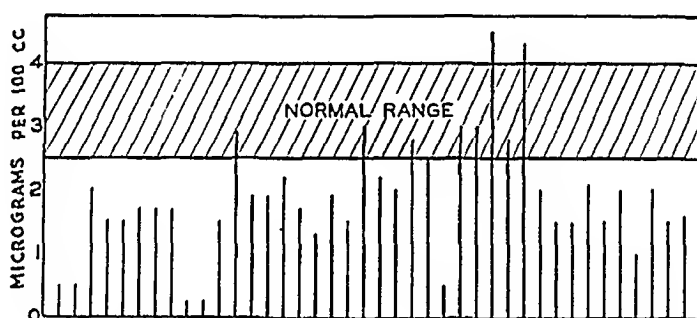


Chart 2—Amount of free thiamine in the blood of 40 thyrotoxic patients

other than that contingent on a basal metabolic rate above  $+20$  per cent and definite clinical evidence of thyrotoxicosis. Five patients had received a few small doses of thiamine, chiefly in the form of yeast. Blood was drawn from the patients when they were in a resting and fasting state. Whenever a tourniquet was used for a venipuncture, an interval of about five seconds was allowed to elapse between release of the tourniquet and withdrawal of blood. Enough blood was drawn at one time for determinations of thiamine, diphosphothiamine, pyruvic acid and lactic acid.

*Thiamine*—Estimations of thiamine was performed by the thiochrome method of Jansen<sup>37</sup> modified by Egana and Robinson.<sup>38</sup> This method depends on the

33 Frazier, W D, and Ravdin, I S. The Use of Vitamin B<sub>1</sub> in the Preoperative Preparation of the Hyperthyroid Patient, *Surgery* 4: 680, 1938.

34 Means, J H. The Thyroid and Its Diseases, Philadelphia, J B Lippincott Company, 1937.

35 Borison, H J. Clinical Application of the Thiochrome Reaction in the Study of Thiamin (Vitamin B<sub>1</sub>) Deficiency, *Ann Int Med* 14: 1, 1940.

36 Dr Herbert Sise, of the Lahey Clinic, gave us the opportunity of studying many of these patients.

37 Jansen, B C P. A Chemical Determination of Aneurin (Vitamin B<sub>1</sub>) by the Thiochrome Method, *Rec d trav chim d Pays-Bas* 55: 1046, 1936.

38 Egana, E, and Robinson, P F. The Estimation of Diphosphothiamin and Thiamin in Blood, to be published.

quantitative oxidation of thiamine to thiochrome, in the presence of alkaline ferricyanide, measurable by the intensity of blue fluorescence in ultraviolet light

Of the 40 specimens of blood studied, 31 had a lower thiamine level than normal (chart 2). We found the range for 25 normal persons to be between 2.5 and 4 micrograms per hundred cubic centimeters.

Borson,<sup>35</sup> using thiamine saturation tests, found evidence of deficiency in all 12 thyrotoxic patients he tested.

*Diphosphothiamine*—Since the biologically active form of thiamine is diphosphothiamine, we estimated the amount of the latter in each of the aforementioned specimens of blood. The method employed was one recently described by Egana and Robinson.<sup>38</sup> It depends on the quantitative conversion of diphosphothiamine to diphosphothiochrome, the latter giving a blue fluorescence in ultraviolet light. The intensity of the fluorescence is compared with that exhibited by a gradient set of standard solutions that have been carried through the same process as the unknown, and thereby the amount of diphosphothiamine estimated. A known amount of thiamine was added to almost every specimen of blood, and the percentage recoverable was determined. In some patients only a small amount

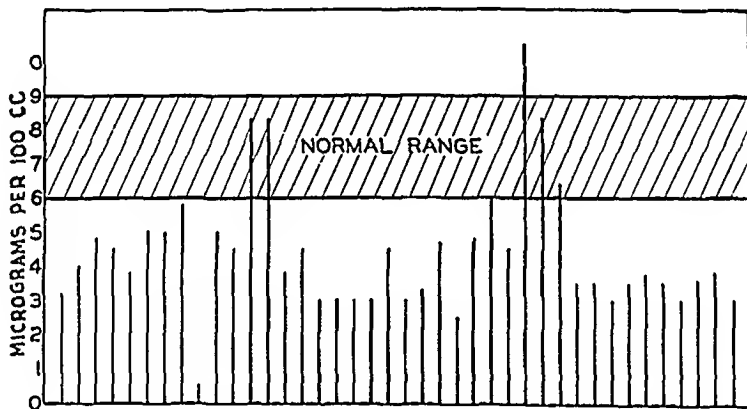


Chart 3—Amount of diphosphothiamine in the blood of 40 thyrotoxic patients

was recovered, but these patients tended to have a high pyruvic acid content in the blood. (This will be discussed later.) A few such patients were followed while receiving treatment with thiamine. As they became saturated with this vitamin and as the diphosphothiamine level of the blood returned to normal, the percentage of vitamin recovered by the technic described tended to return to normal.

The diphosphothiamine content of the blood of 25 normal persons in a resting and fasting state was found to be between 6 and 9 micrograms per hundred cubic centimeters. However, the amount of this substance was below the normal level in 34 of the 40 thyrotoxic patients examined (chart 3). Furthermore, in the majority of cases the reduction was moderate. The amount of free and of phosphorylated thiamine tended to parallel each other, although in a few instances there were distinct discrepancies. For example, the patients with diphosphothiamine levels, respectively, of 3 to 4, 4 to 5.5 and above 5.5 micrograms per hundred cubic centimeters had average thiamine levels of 1.1, 1.6 and 3 micrograms per hundred cubic centimeters. It was our impression that the determinations of diphosphothiamine were a little more accurate than those of thiamine. Furthermore, on following some patients from day to day, we did not observe quite as much fluctuation in the phosphorylated form.

When the thyrotoxic subjects were considered as a group, there was no correlation between the amount of vitamin B deficiency and the height of the basal metabolic rate or the duration of the disease. However, when the subjects were considered individually, these factors were significant, as was, of course, the food eaten.

*Pyruvic Acid*—When the blood was collected for the thiamine determinations about 6 cc. was placed in a bottle with 0.2 cc. of 30 per cent sodium monoiodoacetate and 1 drop of 20 per cent potassium oxalate solution. The use of the iodoacetate was based on the experiments of Bueding and Wortis,<sup>39</sup> which showed that this substance would prevent the disappearance of pyruvic acid from the blood. These investigators also found that if blood to which sodium monoiodoacetate had been added was allowed to stand at room temperature for thirty minutes, an increase of pyruvic acid of 3 to 20 per cent was observed. On the other hand, if blood was precipitated at intervals ranging from forty seconds to ten minutes after withdrawal from the vein, significant losses were observed when the stabilizing medium was not used. Our observations confirm these principles, however, we did not notice significant changes in pyruvic acid if the blood was kept in the ice box for thirty minutes or more before precipitation.

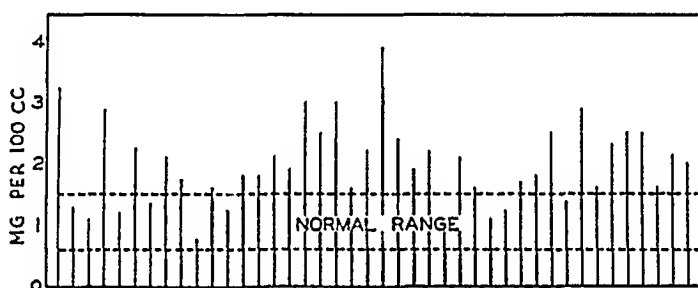


Chart 4—Amount of pyruvic acid in the blood of 42 thyrotoxic patients

We used the Lu<sup>40</sup> method for the determination of pyruvic acid with essentially the modifications described by Bueding and Wortis<sup>39</sup>. This method depends on the conversion of pyruvic acid into its hydrazone by the use of 2,4-dinitrophenylhydrazine, the extraction of this substance with ethyl acetate, the use of sodium carbonate for the separation of the pyruvate hydrazone from the excess hydrazine and the hydrazones of other ketones and aldehyde derivatives, and the quantitation in a photoelectric colorimeter of the red color produced by the addition of sodium hydroxide.

We have found that the level of pyruvic acid of the blood during fasting in most normal persons is between 0.5 and 1.5 mg. per hundred cubic centimeters and usually not below 1 mg.; rarely, it is slightly above 1.5 mg. This is in essential agreement with the results of Johnson<sup>41</sup>. However, our normal values are higher than the ones obtained by Lu<sup>42</sup> and slightly higher than the ones of Bueding and Wortis<sup>39</sup>.

39 Bueding, E., and Wortis, H. The Stabilization and Determination of Pyruvic Acid in the Blood, *J. Biol. Chem.* **133**: 585, 1940.

40 Lu, G. D. XXX Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B<sub>1</sub> Deficient States. I. A Rapid, Specific and Sensitive Method for the Estimation of Blood Pyruvate, *Biochem. J.* **33**: 249, 1939.

41 Johnson, R. Personal communication to the authors.

42 Lu, G. D. Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B<sub>1</sub> Deficient States. II. Blood Pyruvate Levels in the Rat, Pigeon, Rabbit and Man, III. The Relation of Blood Pyruvate to Cardiac Changes, *Biochem. J.* **33**: 774, 1939.

The pyruvic acid content of the blood was elevated in 32 of 42 thyrotoxic patients whom we examined. Within a wide range, there was a definite correlation of this change with the amount of diphosphothiamine present. For example, all 21 patients with a diphosphothiamine level below 4 micrograms per hundred cubic centimeters had a pyruvic acid level above 2 mg per hundred cubic centimeters, and 11 patients with a diphosphothiamine level below 3.5 micrograms had a pyruvic acid level averaging 2.7 mg. On the other hand, none of the patients with a diphosphothiamine level above 5 micrograms per hundred cubic centimeters had a pyruvic acid level above 1.8 mg per hundred cubic centimeters. These results support the conclusions of Lu<sup>42</sup> and of Bueding, Wortis and Stern<sup>43</sup> that the pyruvic acid content of the blood is elevated in practically all cases of definite vitamin B<sub>1</sub> deficiency and is of aid in the diagnosis and the evaluation of the course of this deficiency.

*Lactic Acid*—Only a few determinations of the lactic acid were performed, since the atmosphere around our hospital contained too many interfering substances for accurate results. The estimations were carried out at the Fatigue Laboratory (Harvard University) with the apparatus and method used by Edwards<sup>44</sup>.

The lactic acid content of the blood was elevated in 5 of 7 thyrotoxic patients in a resting and fasting state. Of 19 determinations on 3 subjects, it was elevated in all but 2 instances, occasionally being as high as 25 to 30 mg per hundred cubic centimeters.

*Magnesium*—Soffer and collaborators<sup>45</sup> found that in 35 of 50 patients with hyperthyroidism there was a definite increase in nondiffusible magnesium. Although the degree of this change was not consistently proportional to the height of the metabolic rate, there was a decrease in the nondiffusible magnesium with adequate iodine treatment, a further decrease with subtotal thyroidectomy and a drop to a subnormal level in myxedema. On the other hand, the administration of thyroid or thyroxin to myxedematous patients or thyroidectomized dogs resulted in a return of the magnesium to normal levels. Laviertes and Dine<sup>46</sup> confirmed these observations and found that in 7 patients with hypermetabolism without hyperthyroidism the protein-bound magnesium was uniformly normal. They suggested that magnesium may be an integral part of the circulating thyroid hormone or of the complex in which the hormone functions.

#### EFFECT ON CARBOHYDRATE METABOLISM OF TREATMENT WITH THIAMINE AND MAGNESIUM

The evidence thus far indicates that in the blood of most thyrotoxic subjects there is an accumulation of pyruvic acid, as well as of lactic acid, a decrease in the diphosphothiamine and an increase in the protein-bound magnesium. Since diphosphothiamine and magnesium are greatly concerned in the decarboxylation

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43 Bueding, E., Wortis, H., and Stern, M. Pathological Variations in Blood and Spinal Fluid Pyruvic Acid, *J Clin Investigation* **21** 85, 1942. Bueding, E., and Wortis, H. Pyruvic Acid in Blood and Cerebrospinal Fluid, *Proc Soc Exper Biol & Med* **44** 245, 1940.

44 Edwards, H. T. A Simplified Estimation of Lactate in Normal Human Blood, *J Biol Chem* **125** 571, 1938.

45 Soffer, L. J., Dantes, D. A., Grossman, E. B., Sobotka, H., and Jacobs, M. D. Ultrafiltrable Magnesium in Hyperthyroidism, *J Clin Investigation* **18** 597, 1939. Soffer, L. J., Cohn, C., Grossman, E. B., Jacobs, M., and Sobotka, H. Magnesium Partition Studies in Graves' Disease and in Clinical and Experimental Hypothyroidism, *ibid* **20** 429, 1941.

46 Laviertes, P. H., and Dine, R. F. The Relation of Magnesium to the Thyroid Hormone, *J Clin Investigation* **20** 444, 1941.

and oxidation of pyruvic acid, as stated, we performed a series of experiments on the effect on the carbohydrate metabolism of the administration of diphosphothiamine and magnesium to 7 patients with thyrotoxicosis, 2 with myxedema, 2 with neuritis associated with vitamin B<sub>1</sub> deficiency and 9 normal persons. The thyrotoxicosis was mild or moderate in 6 patients and severe in 1.

Changes in the levels of dextrose, pyruvate, lactate, thiamine and diphosphothiamine in the blood were observed at frequent intervals during a period of four hours following the injection of dextrose. The experiment was repeated several times, in order that we might observe these chemical changes after the injection of dextrose plus magnesium, dextrose plus magnesium plus diphosphothiamine, dextrose plus diphosphothiamine and diphosphothiamine without dextrose. The entire group of experiments was performed on some patients and only a few on others. Thus, not only were the responses in the different types of patients compared, but each patient served as a control for himself.

All the subjects had been receiving a high carbohydrate intake before the tests were carried out, and an interval of at least two to three days was permitted to elapse between tests. The patients were kept in a fasting and resting state while the experiments were performed. The specimens of blood were obtained from the arm which had not received the injections.

*Effects of the Injection of Dextrose*—Fifty grams of dextrose in 50 per cent solution was injected intravenously over a period of six minutes. Specimens of blood were usually taken at the following times: during fasting and fifteen, forty-five, ninety, one hundred and fifty minutes and four hours after the administration of the dextrose.

For 3 of the thyrotoxic patients the dextrose tolerance curve was normal, but for the other 4 there were an elevated fasting level and a slower fall than normal, all of the dextrose levels determined forty-five, ninety and one hundred and fifty minutes after the injection of dextrose were above those of the normal persons at the corresponding times. The averages of these results have been plotted in chart 5. The dextrose tolerance curves of the myxedematous patients were almost identical with those of the thyrotoxic patients (chart 5) except that the specimens taken during fasting were normal. Of the 2 thiamine-deficient patients, 1 had a decreased dextrose tolerance, whereas the other had a normal response.

For a number of years it has been known that thyrotoxic subjects tend to show a decreased tolerance to dextrose.<sup>47</sup> It is not entirely clear as to why this is true, although a number of factors may be considered as possibly playing a role, e. g., starvation, vitamin B deficiency, hepatic damage and concomitant disease of the pituitary or pancreas.

John<sup>48</sup> found that diabetes was twice as common in patients with hyperthyroidism as in the general population, but in 38.7 per cent of the former the dextrose tolerance curve ultimately returned to normal, whereas it became normal in only 29.6 per cent of persons without hyperthyroidism. He noted that all of the thyrotoxic patients who had a normal dextrose tolerance curve before thyroidectomy continued to have a normal one indefinitely. The demonstration of the decreased dextrose tolerance in these patients long after thyroidectomy suggests that the pancreatic islets may have been exhausted, owing to the continued heavy demands placed on them, or that there is a persistence of hypertutary activity.

47 Youmans, J. B., and Warfield, L. M. Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, *Arch. Int. Med.* **37**:1 (Jan.) 1926.

48 John, H. J. Repeated Glucose Tolerance Tests in Hyperthyroidism, *J. Clin. Endocrinol.* **2**:264, 1942.

Bueding, Stein and Wortis<sup>49</sup> found a decreased dextrose tolerance in most patients with vitamin B<sub>1</sub> deficiency. We were unable to alter the dextrose tolerance curve of any of our patients by giving 5 mg of diphosphothiamine intravenously just before performing the dextrose tolerance tests. It is of interest that 1 patient who repeatedly showed decreased dextrose tolerance had a normal response to dextrose after a thyroidectomy in spite of evidence of a moderate deficiency in vitamin B<sub>1</sub>.

Weller<sup>50</sup> found a well marked chronic parenchymatous hepatitis in 22 of 44 selected patients with exophthalmic goiter, but only 1 example of the same degree of change was found in a control series of the same number of persons studied at autopsy. In fact, only 6 of the patients showed no hepatitis, whereas of the control series 30 of the total 44 showed no hepatitis. Furthermore, Youmans and Warfield<sup>47</sup> demonstrated an impairment of hepatic function in 50 per cent of the patients with thyrotoxicosis on whom they performed tests. They also found that 21 of 27 patients showed a decreased dextrose tolerance, but they stated that this, more than any other feature of the disease except loss of weight, was found to be related to the decreased efficiency in hepatic function.

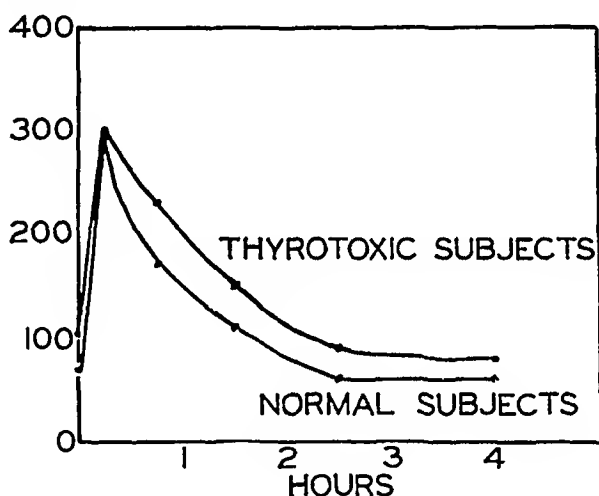


Chart 5—Blood sugar curves (average) after the intravenous injection of 50 Gm of dextrose in normal and in thyrotoxic subjects

Vitamin B<sub>1</sub> deficiency, hepatic disease, depletion of the glycogen stores of the body and associated disease of the pituitary and pancreas probably account for many of the disturbances in the dextrose tolerance reactions that have been observed in thyrotoxic patients.

The changes in the level of pyruvic acid in the blood following infusion of dextrose were pronounced in all 7 thyrotoxic subjects. A marked rise occurred (chart 6) immediately after injection of the dextrose, and the level continued to rise for thirty to forty-five minutes, reaching a peak of 3 to 5 mg per hundred cubic centimeters. The level was highest in 2 subjects at ninety minutes. In all but 1 subject it was still elevated at the end of one hundred and fifty minutes. However, in 7 normal persons tested it did not rise above 2.5 mg per hundred cubic centimeters at any time and was essentially normal within ninety minutes. There was little rise in the pyruvate curve for the 2 myxedematous patients tested, the highest level being 1.9 mg per hundred cubic centimeters. The response in

49 Bueding, E., Stein, M. H., and Wortis, H. Blood Pyruvate Curves Following Glucose Ingestion in Normal and Thiamine Deficient Subjects, *J Biol Chem* **140** 697, 1941.

50 Weller, C. V. Hepatic Lesions Associated with Exophthalmic Goiter, *Tr A Am Physicians* **45** 71, 1930.

the patients with vitamin B<sub>1</sub> deficiency was similar to that in the thyrotoxic patients Bueding, Stein and Worts<sup>40</sup> have reported that in subjects with thiamine deficiency the level of pyruvate in the blood during fasting is elevated and that the pyruvate curve after ingestion of dextrose is abnormally elevated and is slow in returning to a normal level

For a further test of the ability of thyrotoxic subjects to metabolize pyruvic acid, 5 Gm of sodium pyruvate was prepared and injected intravenously according to the technic described by Wilkins, Weiss and Taylor<sup>51</sup> Again it was demonstrated that these patients metabolize pyruvic acid distinctly more slowly than normal

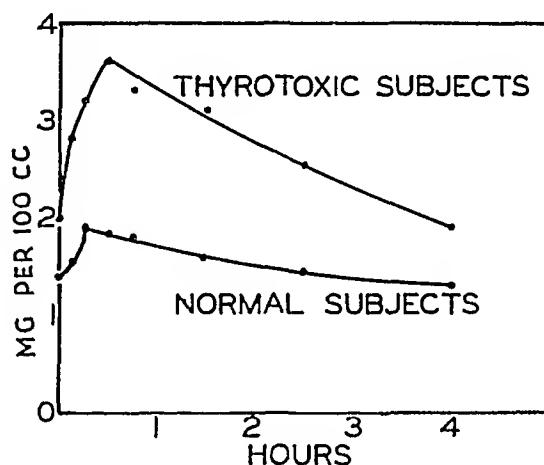


Chart 6—Pyruvic acid curves (average) after the injection of dextrose in 8 normal and in 6 thyrotoxic subjects

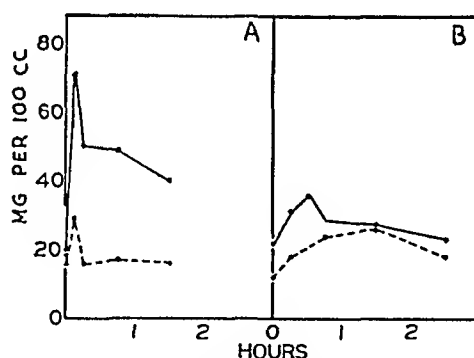


Chart 7—Lactate curves (average) after the injection of sodium pyruvate (A) or dextrose (B) in 4 normal subjects (broken lines) and in 5 thyrotoxic patients (unbroken lines)

We found that in the thyrotoxic subjects, regardless of whether dextrose or sodium pyruvate was injected, the lactate of the blood rose to abnormally high levels and was slow in returning to normal (chart 7)

For four hours after the injection of dextrose the levels of diphosphothiamine and thiamine in the blood showed moderate fluctuation. However, the amount of these substances remained at definitely lower levels in the thyrotoxic subjects than in the normal persons (chart 8)

*Effects of the Injection of Dextrose and Magnesium*—In order to study the effects of the decreased amounts of diffusible magnesium on the abnormal pyruvic

51 Wilkins, R. W., Weiss, S., and Taylor, F. H. L. The Effect and Rate of Removal of Pyruvic Acid Administered to Normal Persons and to Patients With and Without "Vitamin B Deficiency," *Ann Int Med* 12 938, 1939

acid metabolism in thyrotoxic subjects, we saturated the patients with magnesium sulfate, repeated the dextrose injection and studied the resulting changes in the values for dextrose, pyruvate, lactate, free thiamine and diphosphothiamine in the blood

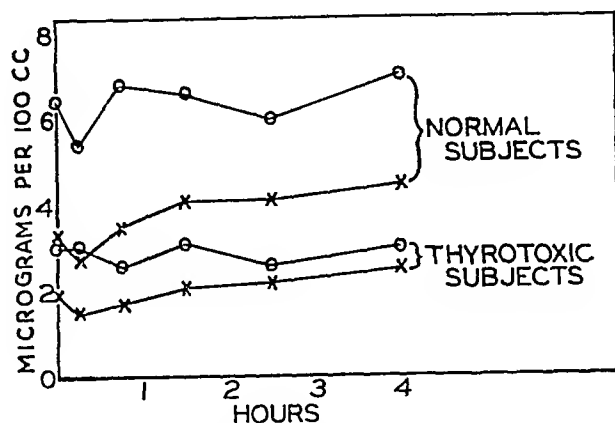


Chart 8—Thiamine (X—X) and diphosphothiamine (O—O) curves (average) after the injection of dextrose in 5 normal subjects and 5 thyrotoxic patients

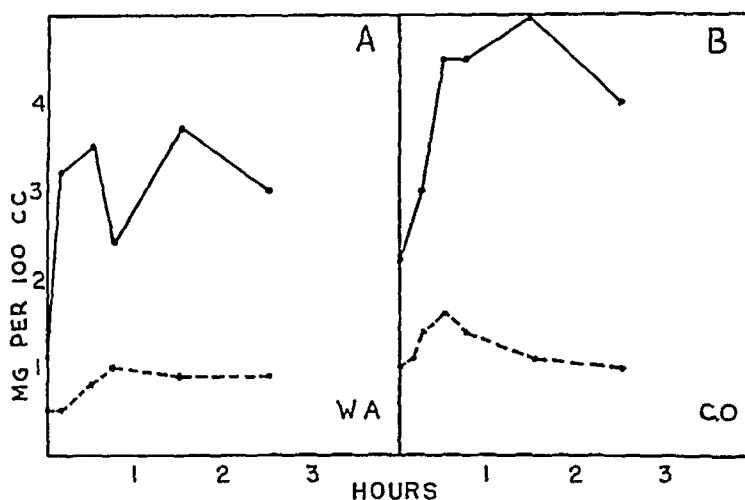


Chart 9—The marked effect of diphosphothiamine in one case (A) and of magnesium sulfate in another (B) in preventing the rise of pyruvic acid after the intravenous injection of 50 Gm of dextrose. The unbroken lines indicate dextrose and the broken lines dextrose plus diphosphothiamine (A) and dextrose plus magnesium sulfate (B)

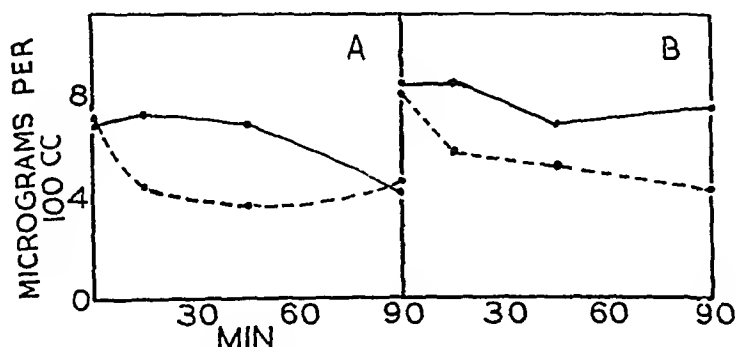


Chart 10—The effect of magnesium sulfate in suppressing the diphosphothiamine curve after the injection of sodium pyruvate or dextrose. In A the unbroken line indicates sodium pyruvate and the broken line sodium pyruvate plus magnesium sulfate. In B the unbroken line indicates dextrose and the broken line dextrose plus magnesium sulfate

One gram of magnesium sulfate in 50 per cent solution was given intramuscularly on the night preceding the test and again at 6 o'clock the next morning



Either 0.5 or 1 Gm was given intravenously immediately before the injection of dextrose. One gram was given about thirty minutes later and again about ninety minutes after the dextrose. The results were compared with those obtained when dextrose alone was injected.

The magnesium was not found to have any effect on the sugar tolerance curves of the thyrotoxic, myxedematous or normal subjects. It had a marked effect in preventing the rise in pyruvic acid content in 1 thyrotoxic patient (chart 9) and in 1 patient deficient in vitamin B but no definite effect on the normal or the myxedematous subjects. It had a slight lowering effect on the blood lactate content of 2 thyrotoxic subjects. There was a tendency for the magnesium to elevate the diphosphothiamine and thiamine curves, although the reverse was true in 2 patients, as shown in the accompanying table. In 1 thyrotoxic patient (chart 10), it was clear in three different experiments that the magnesium lowered the diphosphothiamine level in the blood. This effect lasted for only about forty-five minutes but another injection was found to lower the level again.

*Effect of Magnesium and Diphosphothiamine*

Subjects		Changes * in the Blood									
		Dextrose			Pyruvate			Lactate			
		Magnesium Sulfate	Diphosphothiamine	Both	Magnesium Sulfate	Diphosphothiamine	Both	Magnesium Sulfate	Diphosphothiamine	Both	Diphosphothiamine Magnesium Sulfate
Thyrotoxic	W A	0	0	0	0	—	—	—	—	—	—
	C O	0	0	0	—	—	—	—	—	—	—
	J L	0	0	0	+	—	—	—	—	—	—
Normal	C D	0	0	0	0	—	0	—	—	—	—
	L E	0	0	0	0	—	0	—	—	—	—
	K I	0	0	0	0	—	0	—	—	—	—
	G A	0	0	0	0	—	0	—	—	—	—
Myxedematous	W E	0	0	0	0	—	0	—	—	—	—
Vitamin B <sub>1</sub> neuritis	O B	0	0	0	0	—	0	—	—	—	—

\* 0 indicates no effect ±, a questionable effect +, an elevating effect, and —, a depressing effect

With 2 thyrotoxic patients the experiment was repeated, magnesium sulfate and 5 Gm of sodium pyruvate being administered intravenously instead of dextrose. The magnesium caused a more rapid disappearance of lactate than did pyruvate alone (chart 11). It also caused a slightly more rapid disappearance of pyruvic acid.

*Effects of the Injection of Dextrose and Diphosphothiamine*—The dextrose experiments were repeated, and immediately after the dextrose was injected 5 mg of diphosphothiamine was given intravenously during a period of two minutes. Samples of blood were taken at the following times: during fasting and six, eight, fifteen, forty-five, ninety and one hundred fifty minutes and four hours after the injection of dextrose was begun. The results were compared with the ones obtained when dextrose alone was administered.

The diphosphothiamine had no effect on the blood sugar content in any subject. It exerted a marked depressing effect on the pyruvic acid of 1 thyrotoxic patient (chart 9) and a slight effect on another thyrotoxic and 1 normal person. It also tended to prevent the rise in the lactate of the blood of the 1 thyrotoxic subject tested.

*Effects of the Injection of Dextrose, Magnesium and Diphosphothiamine*—The experiment was repeated, magnesium sulfate, dextrose and diphosphothiamine being given in the same manner as in the other experiments. However, these substances had no effect on the dextrose tolerance curve of any patient except the one with vitamin B<sub>1</sub> deficiency, in whom a lowering occurred. In this patient, as well as in 2 thyrotoxic ones, there was less accumulation of pyruvic acid in the blood than in the experiments in which dextrose alone was used. In 2 thyrotoxic subjects the magnesium and diphosphothiamine tended to prevent some of the rise in lactate content.

*Effects of the Injection of Diphosphothiamine*—When 5 mg of diphosphothiamine was given alone, intravenously, to 5 normal persons the pyruvic acid content of the blood rose from 0.3 to 0.8 mg per hundred cubic centimeters above the fasting level within eight minutes but began to decline within fifteen minutes and was normal in forty-five minutes. However, of 3 thyrotoxic patients tested, in 1 the value for pyruvic acid simulated the normal, in 1 it rose from 1.3 mg to 2 mg per hundred cubic centimeters within fifteen minutes and remained there for two and one-half hours, while in the third it was 2.5 mg per hundred cubic centimeters during fasting, dropped to 2.2 mg in eight minutes and gradually rose

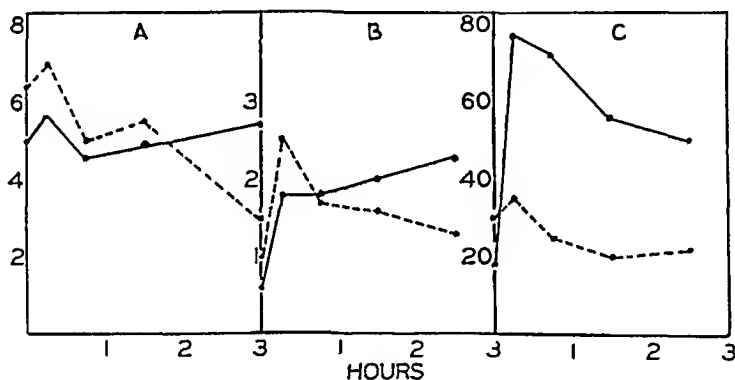


Chart 11—The slight effect of magnesium on the diphosphothiamine (A) and pyruvate (B) curves and the marked effect on the lactate curve (C) after the administration of sodium pyruvate to 1 patient. The unbroken lines indicate sodium pyruvate and the broken lines sodium pyruvate plus magnesium sulfate. The diphosphothiamine is expressed in micrograms per hundred cubic centimeters and the pyruvate and lactate in milligrams per hundred cubic centimeters.

to the fasting level in the subsequent four hours. The diphosphothiamine had slight, if any, lowering effect on the blood sugar content of either the normal or the thyrotoxic subjects.

*Summary*—Thus, magnesium and diphosphothiamine had definite effects on the levels of pyruvic acid, lactic acid, diphosphothiamine and thiamine in the blood. The effects varied in the different patients, although the same type of response was obtained repeatedly in the same person.

#### THIAMINE IN THE TREATMENT OF THYROTOXICOSIS

Means, Hertz and Lerman<sup>6</sup> have observed that the administration of vitamin B improves the clinical state of thyrotoxic subjects, although it does not have any definite effect on the basal metabolic rate. Frazier and Ravdin<sup>33</sup> have made similar observations. They found that when the vitamin B complex was used, there was a greater reduction in the pulse rate, a more rapid gain in weight and a shorter preoperative period.

During the last four years one of us (R H W) has routinely prescribed brewers' yeast, 5 Gm daily, and usually thiamine hydrochloride, 10 to 20 mg daily, for all thyrotoxic subjects observed. The results confirm the ones described herein. Furthermore, the patients were found to experience a distinct subjective improvement.

Mild vitamin deficiencies commonly occur in thyrotoxicosis, and occasionally one sees severe ones. The latter tend to be resistant to treatment. For example, one of us (R H W) has observed 4 thyrotoxic patients with coexisting pellagra, 2 with beriberi, one with neuritis and 2 with riboflavin deficiency, and to these patients it was necessary to give several times the dose of vitamins which one would have expected to give had they not had thyrotoxicosis.

To study this matter further we conducted thiamine balance studies with 5 thyrotoxic patients. In 4 of these patients the disease was mild, or moderate, and in the other it was severe. Each patient was kept in a metabolism ward but spent only part of the time in bed. The diets contained approximately 1 to 2 mg of thiamine. Water was given as desired, and a record of the fluid intake and output

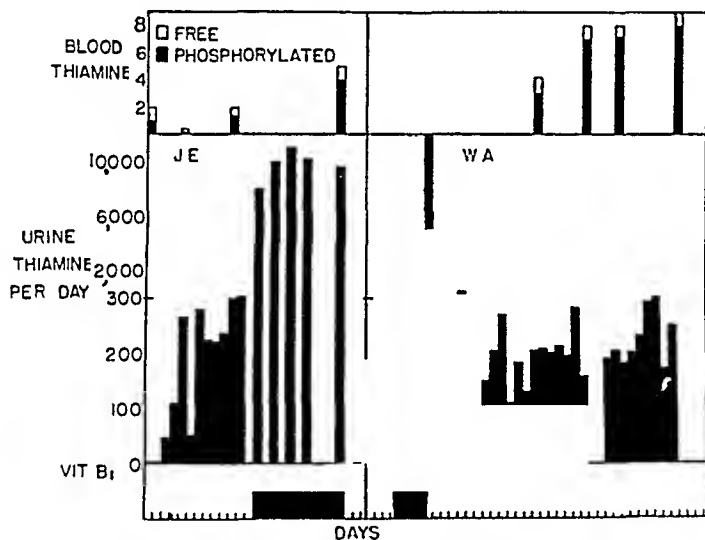


Chart 12—Large amount of thiamine (milligrams) in the urine (cubic centimeters) in spite of the low thiamine and diphosphothiamine content (micrograms per hundred cubic centimeters) of the blood in 2 patients with thyrotoxicosis. The dose of vitamin B<sub>1</sub> was 10 mg of thiamine hydrochloride twice daily given parenterally.

was kept. Total twenty-four hour specimens of urine were collected in 10 cc of glacial acetic acid, and determinations of the thiamine content were performed according to the method of Egana and Meiklejohn.<sup>52</sup>

During the first two days, 4 subjects showed a daily excretion of thiamine in the urine of over 80 micrograms, but the other showed only traces. However, in spite of the fact that the urinary excretion of the vitamin was normal in 4 patients, the levels of diphosphothiamine and free thiamine in the blood were definitely low in each subject. These patients continued to excrete thiamine in the urine daily in quantities of about 200 micrograms in spite of a low level of thiamine in the blood (chart 12).

When 10 mg of thiamine hydrochloride was given parenterally twice daily it was found that after about six to ten days the thiamine content of the blood became normal. However, 1 patient with hyperthyroidism was deficient after twelve

<sup>52</sup> Egana, E, and Meiklejohn, A. P. The Estimation of Thiamine in Urine, *J Biol Chem* **141** 859, 1941.

days of such treatment (chart 12), and in 2 of the others the thiamine returned to a deficient level when the diet was not supplemented with vitamin B<sub>1</sub>. This constant tendency for thyrotoxic patients to become deficient is due not only to the rapid destruction of this vitamin but to its loss in large quantities in the urine, sweat and stools.

Hardt and Still<sup>53</sup> have shown that when there is marked hyperhidrosis significant quantities of thiamine may be lost in the sweat. Since sweating is so common, and often marked, in thyrotoxic patients, it is probable that this accounts partially for the deficiency in thiamine in these persons.

Light, Schultz, Atkins and Cracas<sup>54</sup> have shown that when rats are in excretion equilibrium while receiving 15 or 515 micrograms of thiamine daily about 30 per cent is excreted in the urine and about 25 per cent in the feces. The total amount excreted in the feces increases in proportion to the intake<sup>55</sup>. Since in thyrotoxic subjects the motility of the gastrointestinal tract is abnormal and occasionally diarrhea is present, an increased fecal excretion of thiamine may be expected.

Just how much destruction of vitamin B<sub>1</sub> occurs in thyrotoxic subjects is not known, but it is probably a large quantity owing to the increased metabolism. Borsook and co-workers,<sup>56</sup> using thiamine containing radiosulfur, have shown that a considerable quantity of injected thiamine is destroyed and excreted in the urine as neutral sulfur compounds and inorganic sulfate. However, in addition to these degradation products there tend to be excess quantities of thiamine in the urine, as we have mentioned before. This is due, as Borson<sup>35</sup> has pointed out, somewhat to the marked diuresis shown by many thyrotoxic patients. In the patients whom we studied the daily excretion of urine averaged from 1,800 to 3,200 cc.

Ordinarily, as the body stores of thiamine become deficient, the quantity of this substance excreted in the urine becomes greatly reduced. For example, as shown in chart 13, 2 normal persons on a normal diet had an average daily excretion of 70 and 50 micrograms of thiamine, respectively. However, when their diet was reduced sufficiently to reduce the blood diphosphothiamine to a low level, 3 micrograms per hundred cubic centimeters, the urinary excretion of thiamine was less than 10 micrograms. On the other hand, a thyrotoxic subject with the same low level of diphosphothiamine in the blood, 3 micrograms, excreted an average of 185 micrograms daily for four days. It may be observed (chart 13) that the urinary volume was about twice as great in the thyrotoxic patient as in the normal subjects.

In addition to the foregoing factors which contribute to thiamine deficiency in thyrotoxic patients, one must consider the storage capacity of the tissues in these patients. Since this vitamin is stored in large part as diphosphothiamine, it is important to know, first, how well they can carry out phosphorylation of thiamine and, second, how well they can store the vitamin after phosphorylation.

We observed from our balance studies that sufficient phosphorylation occurred in the patients to permit a normal level of diphosphothiamine to develop in the blood within a period of about ten days. We also found that two minutes after

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53 Hardt, L. L., and Still, E. N. Thiamin in Sweat, *Proc Soc Exper Biol & Med* **48** 704, 1941.

54 Light, R. F., Schultz, A. S., Atkins, L., and Cracas, L. G. The Excretion of Vitamin B<sub>1</sub> in the Urine and Feces, *J Nutrition* **16** 333, 1938.

55 Leong, P. C. Vitamin B<sub>1</sub> in the Animal Organism. II. A Quantitative Study of the Metabolism of Vitamin B<sub>1</sub> in Rats, *Biochem J* **31** 373, 1937.

56 Borsook, H., Buchman, E. R., Hatcher, J. B., Yost, D. M., and McMillan, E. The Course of Thiamin Metabolism in Man as Indicated by the Use of Radioactive Sulfur, *Proc Nat Acad Sc* **26** 412, 1940.

the intravenous injection of 5 mg of thiamine hydrochloride there was a marked rise in the diphosphothiamine content of the blood. No doubt many patients with thyrotoxicosis have more hepatic damage than did the ones we were working with, but we have demonstrated that in patients with severe Laennec's cirrhosis the phosphorylation of thiamine readily takes place. The liver is one of the main storehouses for thiamine. Therefore, since one often finds evidence of hepatic damage, the quantity of thiamine available in the body is probably reduced.

While the studies on thiamine balance were being performed on the patients previously mentioned as well as on 1 other patient, the basal metabolic rate and the weight of each patient were carefully followed, but these tended to remain the same.

Since 1 thyrotoxic patient noticed a feeling of well-being and marked relaxation after an injection of magnesium sulfate, it was decided to observe the effect of this substance on the basal metabolic rate. She was given 1 Gm of magnesium

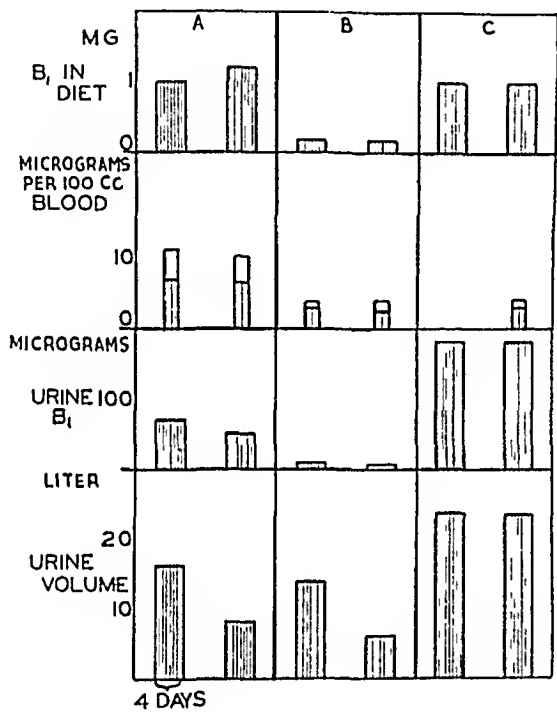


Chart 13—*A* shows the values for 2 normal persons on a normal diet, *B*, the values for the same persons after they had been on a thiamine-deficient diet for several days (a diphosphothiamine content of the blood of only 3 micrograms per hundred cubic centimeters and a daily excretion of thiamine in the urine of about 15 micrograms), *C*, the values for a thyrotoxic patient, who had an equally low diphosphothiamine content of the blood but excreted about 185 micrograms daily. Each of the broad columns represents an average daily value for an interval of four days. The shaded blocks indicate diphosphothiamine and the clear portions thiamine.

sulfate intramuscularly three times daily for six days. No change in the metabolic rate was observed. Similar treatment of a myxedematous patient likewise was found to have no appreciable effect.

### SUMMARY AND CONCLUSIONS

The interrelationship of cellular oxidations and the functions of the thyroid gland are discussed.

In the majority of a group of 40 unselected thyrotoxic subjects the levels of free thiamine and diphosphothiamine in the blood were below normal and that of pyruvic acid was elevated. In 5 of 7 of these patients the level of lactic acid was

elevated The thiamine deficiency was regarded as being due to the waste of this substance in the stools, sweat and urine, as well as to the excessive combustion of food Thyrotoxic patients tend to excrete relatively large amounts of thiamine in the urine in spite of a deficiency of this substance in the blood The excessive excretion of thiamine in the urine is due partially to the diuresis which these patients experience It is possible that thyrotoxic subjects cannot store as much thiamine as normal subjects because of the often coexisting hepatic and muscular disease However, no impairment of the phosphorylation of thiamine was demonstrable

During a period of four hours following the intravenous injection of 50 Gm of dextrose or 5 Gm of sodium pyruvate, the levels of pyruvic acid and lactic acid in the blood remained distinctly higher in thyrotoxic subjects than in normal persons The response of the thiamine and diphosphothiamine in the blood varied, but these substances tended to remain at lower levels in thyrotoxic subjects than in normal ones

Since patients with hyperthyroidism tend to have a decreased amount of diffusible magnesium and diphosphothiamine in the blood, the experiments with dextrose or sodium pyruvate were repeated immediately after 5 mg of diphosphothiamine had been given or the patient had been saturated with magnesium sulfate These substances had essentially no effect on the blood sugar content but in some instances had a marked effect on the blood pyruvate and lactate

Administration of thiamine hydrochloride is of distinct advantage as an adjunctive measure in the treatment of thyrotoxicosis

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# A MODIFIED TECHNIC FOR THE DETERMINATION OF SERUM BILIRUBIN

A PRELIMINARY REPORT OF ITS CLINICAL USE

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In a previous paper we<sup>1</sup> presented a modified technic for the determination of serum bilirubin. This technic possesses several technical advantages over the methods commonly in use and gives a more accurate evaluation of the concentration of the pigment. Furthermore, by this method the direct and indirect fractions can be measured separately. In this paper the results obtained from the clinical application of the new technic will be presented.

The method was used in a study of the behavior of the serum bilirubin of four different groups of persons: (1) normal persons and patients without evidence of hepatic disease, (2) patients who had hepatic disease but no jaundice, (3) patients in whose cases the result of the determination of the concentration of serum bilirubin and the result of the bromsulfalein test of hepatic function did not agree as to the presence of probable or proved hepatic disease and (4) patients who had parenchymatous, obstructive or hemolytic jaundice. The third group was included in order to study the correlation between the results of the bromsulfalein test and the values of indirect-reacting bilirubin in a small number of cases in which hepatic disease was suspected or proved to be present.

## VALUES FOR BILIRUBIN IN THE SERUM OF NORMAL PERSONS AND PATIENTS WITHOUT DISEASE OF THE LIVER

The concentrations of bilirubin in the serum of 22 healthy technicians, nurses and physicians and in that of 63 patients who did not present clinical or laboratory evidence of hepatic disease were determined. Bilirubin giving the direct van den Bergh reaction was not found in the serum of any person in these two groups. The percentage incidence of each of the various concentrations of bilirubin giving the indirect van den Bergh reaction is shown in table 1. The concentrations varied from 0.1 to 0.8 mg per hundred cubic centimeters of serum, but it should be emphasized that the values for bilirubin giving the indirect reaction were less than 0.6 mg per hundred cubic centimeters in 95.5 per cent of cases.

## VALUES FOR SERUM BILIRUBIN IN CASES OF HEPATIC DISEASE WITHOUT JAUNDICE

Values for serum bilirubin in 23 cases of disease of the liver without jaundice were determined (table 2). There were 12 cases of cirrhosis of the liver, 5 cases of myocardial failure and 6 cases of metastatic involvement of the liver. Bilirubin giving the direct van den Bergh reaction was not detected in any of these cases. In 10 of the 23 cases the concentration of bilirubin in the serum was more than

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In this study Miss Elizabeth MacLay gave much technical assistance.

<sup>1</sup> Sepulveda, B., and Osterberg, A. E. Serum Bilirubin. A Procedure for the Determination of Indirect and Direct Values, J. Lab. & Clin. Med., to be published.

the upper limit (0.8 mg per hundred cubic centimeters) of the range encountered in normal persons and patients who did not have hepatic disease. It was within the range (0.1 to 0.8 mg per hundred cubic centimeters) found for persons without hepatic disease in the remaining 13 cases but the values in 11 of the 13 cases fell within the upper part of the range (0.6 to 0.8 mg per hundred cubic centimeters) in which only 4.5 per cent of the values for persons without hepatic disease fell. In only 2 of the 23 cases were the values within the range (0.1 to 0.5 mg per hundred cubic centimeters) of values in which 95.5 per cent of the values for persons without hepatic disease fell. Concentrations of bilirubin of more than 0.8 mg per hundred cubic centimeters of serum are definitely abnormal, those of more than 0.5 mg may be and probably are elevated above normal. Hepatic disease apparently may cause retention and increased concentration of bilirubin giving the indirect van den Bergh reaction without the appearance in the serum of bilirubin giving the direct reaction.

TABLE 1—*Concentrations of Bilirubin Giving the Indirect van den Bergh Reaction in the Serums of Eighty-Five Persons Without Hepatic Damage\**

Bilirubin, Mg per 100 Cc	Percentage of 85 Cases
0.1	9.3
0.2	11.6
0.3	22.0
0.4	27.9
0.5	24.4
0.6	2.3
0.7	1.1
0.8	1.1

\* In 45 cases of this series the bromsulphalein test was carried out and gave negative results.

TABLE 2—*Concentrations of Bilirubin Giving the Indirect van den Bergh Reaction in the Serum in Twenty-Three Cases of Disease of the Liver in Which Bilirubin Giving the Direct Reaction Was Not Present*

Bilirubin, Mg per 100 Cc	Cases
0.0 to 0.2	1
0.3 to 0.4	1
0.5 to 0.6	
0.7 to 0.8	11
0.9 to 1.0	4
1.1 to 1.2	3
1.3 to 1.4	1
1.5 to 1.6	2

In the normal state the balance between the production of bilirubin and its excretion by the liver is constant. The concentration of bilirubin in the serum of a normal person remains low and fluctuates in a narrow range. This balance between production and excretion of bilirubin is altered by a rise of the level of bilirubin giving the indirect van den Bergh reaction in two types of disorder. The first is hemolytic jaundice in which the overproduction of bilirubin giving the indirect reaction surpasses the excretory capacity of the liver. The second is hepatic damage. In this condition the formation of pigment is within normal limits but its excretion by hepatic cells is impaired. The increased quantity of serum bilirubin giving an indirect van den Bergh reaction in hemolytic conditions is well known, but little attention has been called to this increase in cases of hepatic injury.

Rozendaal, Comfort and Snell,<sup>2</sup> using the Thannhauser and Andersen technic for the determination of bilirubin in the serum, have reported the elevation of values for bilirubin giving the indirect reaction in cases of hepatic damage similar

2 Rozendaal, H. M., Comfort, M. W., and Snell, A. M. Slight and Latent Jaundice, J. A. M. A. 104: 374-379 (Feb. 2) 1935.



to those we studied. The new technic for the determination of values for bilirubin, which permits accurate measurement of small increases, provides definitely greater diagnostic possibilities from the study of bilirubin giving the indirect reaction than did the Thannhauser and Andersen technic. This study and our studies point to the possibility, and additional studies may prove, that an increase in the concentration of bilirubin giving an indirect reaction to more than 0.8 mg and possibly to more than 0.5 mg (modified technic) per hundred cubic centimeters of serum is an indication of injury to the liver when the relatively rare hemolytic and the familial type of jaundice have been excluded.

IS IT POSSIBLE THAT AN ELEVATION OF INDIRECT BILIRUBIN REVEALS  
HEPATIC DYSFUNCTION WHEN THE BROMSULPHALEIN TEST  
OF HEPATIC FUNCTION DOES NOT?

In order to obtain an answer to this question, determinations both of the concentration of bilirubin and of the retention of dye in the bromsulphalein test of hepatic function were made in a series of cases in which hepatic damage was suspected or proved. In none of these cases was bilirubin giving the direct van

TABLE 3—*Values for Indirect-Reacting Bilirubin in Nine Cases in Which the Bromsulphalein Test of Hepatic Function Was Negative for Retention and Direct-Reacting Bilirubin Was Not Present*

Diagnosis	Bilirubin Indirect Reaction, Mg per 100 Cc
Carcinoma of liver	0.9
Chronic alcoholism	0.8
Indeterminate splenomegaly	0.7
Residual infection of biliary tract	0.9
Chronic alcoholism	0.8
Chronic hepatitis	0.8
Gout	0.8
Myocardial failure	0.7
Chronic alcoholism	1.2

den Bergh reaction present. In about half of the cases in this group the bromsulphalein test did not disclose retention of dye, these are listed in table 3. In the other half of the group the bromsulphalein test revealed retention of dye and hepatic dysfunction, and these are listed in table 4.

In all the cases listed in table 3 the concentration of bilirubin was more than 0.6 mg per hundred cubic centimeters of serum, that is, above the range of values (0.1 to 0.5 mg, inclusive, per hundred cubic centimeters) encountered in 95.5 per cent of persons who did not have hepatic disease. In 3 of the 9 cases listed in table 3 the values were above the upper limit (0.8 mg) of the values of persons without hepatic disease. In short, while the values for bilirubin were not greatly elevated, they were definitely within the range indicating retention of bilirubin and possible hepatic damage, as was suggested by clinical appraisal in most of these cases. The bromsulphalein test, however, failed to disclose hepatic damage. In the cases listed in table 4 the values for bilirubin were within the range (0.1 to 0.5 mg, inclusive, per hundred cubic centimeters of serum) of 95.5 per cent of persons without hepatic disease and did not suggest hepatic damage, while the bromsulphalein test disclosed retention of dye as was expected from clinical appraisal in most of the cases.

It is clear that the two functions of the liver, the excretion of bilirubin and that of dye, do not behave in a parallel fashion and that bilirubin may be retained in the serum by damage to the liver when dye is not and vice versa. While

Snell and Magath<sup>3</sup> have shown that the bromsulphalein test is one of the most reliable tests of hepatic function in the absence of jaundice, it has been recognized that the test fails at times to reveal damage to the liver. The determination of the concentration of indirect-reacting bilirubin may prove to be a valuable accessory to the bromsulphalein test in the detection of damage of the liver in cases in which jaundice is not encountered and the direct-reacting bilirubin is not present.

#### VALUES OF BILIRUBIN IN CASES OF VARIOUS TYPES OF JAUNDICE

Values for bilirubin giving both the direct and the indirect van den Bergh reaction were determined in 25 cases of intrahepatic jaundice, 40 cases of obstructive jaundice, 8 cases of congenital hemolytic icterus, 1 case of so-called familial jaundice and 1 case of pernicious anemia with jaundice. Bilirubin giving the

TABLE 4—*Values for Indirect Reacting Bilirubin in Ten Cases in Which the Bromsulphalein Test of Hepatic Function Showed Function to Be Abnormal and Direct-Reacting Bilirubin Was Not Present*

Diagnosis	Bilirubin, Indirect Reaction, Mg per 100 Cc	Bromsulphalein Test, Grade *
Chronic alcoholism	0.4	2
Chronic alcoholism	0.5	1
Gout	0.4	1
Inoperable gastric carcinoma	0.5	1
Hyperthyroidism	0.5	1
Chronic alcoholism	0.3	2
Abdominal carcinomatosis involving liver	0.2	2
Chronic alcoholism	0.3	1
Gastric carcinoma, liver metastasis (?)	0.3	3
Gout	0.3	2

\* Grading is on a basis of 1 to 4 in which 1 indicates minimal and 4 maximal retention of dye.

TABLE 5—*Comparison of Values for Serum Bilirubin in Cases of Intrahepatic and Cases of Obstructive Jaundice*

	Cases	Bilirubin, Mg per 100 Cc			
		Direct Reaction		Indirect Reaction	
		Range	Average	Range	Average
Intrahepatic jaundice	25	1.9-7.0	14.7	0.4-5.0	1.8
Obstructive jaundice	40	1.2-9.3	18.6	0.1-10.0	1.9

indirect reaction only was found in the cases of hemolytic jaundice by the new modified technic, while in 5 of these cases the van den Bergh reaction was reported direct when the Thannhauser-Andersen technic was used. The not infrequent confusion in diagnosis arising from such falsely direct van den Bergh reactions is eliminated by the modified technic used in this study.

Bilirubin giving both the indirect and the direct van den Bergh reaction was measurable in every case of intrahepatic and every case of obstructive jaundice. The ranges of values and the average values for both tests of bilirubin in the cases of intrahepatic and the cases of obstructive jaundice are given in table 5. Several investigators, including Varela Fuentes and Viana,<sup>4</sup> Bengolea, Velasco Suárez and Raíces<sup>5</sup> and Franke,<sup>6</sup> among others, have stated that the separate

3 Snell, A. M., and Magath, T. B. The Use and Interpretation of Tests for Liver Function, *J. A. M. A.* **110** 167-174 (Jan 15) 1938.

4 Varela Fuentes, B., and Viana, C. Les bilirubines, directe et indirecte du serum dans les ictères aigus fébriles et dans les ictères chroniques, *Compt. rend. Soc. de biol.* **116** 1187-1192, 1934.

determination of bilirubin giving the direct and of bilirubin giving the indirect reaction is useful in the differential diagnosis of obstructive and of intrahepatic jaundice. These authors assumed that the damage to the hepatic parenchyma impaired the excretion of bilirubin and raised the concentration of this fraction in the serum more than obstructive jaundice. We have been unable to confirm their results with our new technic. In our cases, obstruction of the common bile duct raised the average concentration of bilirubin giving the indirect reaction to 1.9 mg per hundred cubic centimeters, while parenchymatous damage to the liver raised the average concentration to 1.8 mg. These average concentrations are so similar that a differential diagnosis between the two types of jaundice could not be made on this basis in our cases. Heilbrun and Hubbard<sup>7</sup> have reported results similar to ours. In our studies, moreover, the highest concentration of bilirubin giving the indirect reaction was found in a case of obstructive jaundice, not in a case of intrahepatic jaundice. The similarity of behavior of bilirubin giving the indirect reaction in the two types of jaundice may be due to the frequent appearance of parenchymatous damage secondary to the obstruction. The diagnostic importance of the concentration of indirect-reacting bilirubin deserves more study in a larger number of cases.

#### SUMMARY AND CONCLUSIONS

A preliminary report of the clinical use of a new technic for the determination of bilirubin in the serum has been made.

The concentrations of bilirubin in the serum of normal persons and of patients who did not have hepatic disease ranged from 0.1 to 0.8 mg per hundred cubic centimeters of serum. The concentrations were 0.5 mg or less in 95.5 per cent of these persons. The van den Bergh reaction of the serum of all these persons was indirect.

Values for bilirubin giving the indirect van den Bergh reaction may be slightly elevated in cases of hepatic disease without jaundice in which serum bilirubin giving the direct van den Bergh reaction is not found, and this rise apparently may indicate hepatic damage when hemolytic jaundice is excluded. The values may be elevated when the bromsulphalein test of hepatic function does not disclose dysfunction of the liver, and the new technic apparently may indicate hepatic dysfunction when the bromsulphalein test does not.

The concentration of bilirubin giving the indirect van den Bergh reaction is increased in obstructive and in intrahepatic jaundice as well as in hemolytic jaundice. The average concentration of bilirubin giving the indirect van den Bergh reaction in our cases of obstructive jaundice was similar to that in our cases of intrahepatic jaundice. The highest concentration of bilirubin giving the indirect van den Bergh reaction in our series was 10 mg per hundred cubic centimeters of serum and was found in a case of obstructive jaundice, whereas the highest concentration in a case of intrahepatic jaundice was 5 mg. From our study it appears that the difference in the height of the concentration of bilirubin giving the indirect van den Bergh reaction in obstructive and in intrahepatic jaundice is not sufficiently distinctive to aid in the differential diagnosis of these two types of jaundice.

5 Bengolea, A. J., Velasco Suarez, C., and Raices, A. E. El dosaje de la bilirrubina directa e indirecta en el suero sanguíneo. Su importancia en cirugía hepato-biliar, *Prensa médica* **23** 85-102 (Jan 8) 1935.

6 Franke, K. Klinische und lebendmikroskopische Untersuchungen der gestörten Leberfunktion. II. Gallenfarbstoffuntersuchungen bei Lebererkrankungen mit Ikterus, *Ztschr f klin Med* **130** 193-221 (March) 1936.

7 Heilbrun, N., and Hubbard, R. S. Measurement of Chloroform-Soluble Fraction of Bilirubin in Persons with Jaundice and Its Significance, *J Lab & Clin Med* **26** 576-581 (Dec) 1940.

# MILESTONES IN THE DIAGNOSIS AND TREATMENT OF GOUT

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Gout is one of the oldest diseases recorded. A description of it is found as early as the fifth century B. C. in the writings of Hippocrates<sup>1</sup>. Despite its antiquity, there is much that is still unknown. The term gout is derived from the Latin *gutta*, a drop. According to Antonius Guainerius,<sup>2</sup> of the faculty of Pavia (fifteenth century), *gutta* signifies a humor that trickles downward from the head on some internal organ. It also indicates an articular pain, because the humor enters the joints in a manner resembling raindrops dripping from trees and housetops. The Greeks called gout *ποδάγρα* (a trap), because it grips the patient's foot as a trap grips the foot of an animal.<sup>3</sup>

The first use of the term *gutta* to designate gout is erroneously credited to Ralph Bocking (Radulphus),<sup>4</sup> who about 1270 wrote a biography of St. Richard of Wyche, bishop of Chichester, England. Bocking, who was the confessor of the bishop, mentioned a servant in the latter's household who was cured of his gout (*gutta quam podagram vel arteticam vocant*) by donning the bishop's boots. However, the word gout appears in earlier writings. Geoffroi de Villehardouin,<sup>5</sup> the famous French historian, used it in his "Histoire de l'empire de Constantinople sous les empereurs françois," written between 1207 and 1212. The author related that the count Hugues de Saint Paul had "a grand malady of gout" (*une grant maladie de gote*) in his feet and knees and that he died of it. Physicians in medieval times were reluctant to use the term.<sup>6</sup> Nevertheless, it does appear in the learned works of prominent members of the Medical School of Salerno in the twelfth century. In a prescription from the *antidotarium* of Nicolaus Salernitanus<sup>7</sup> it is stated that *benedicta*, which contains hermodactyl as an ingredient, is of value for arthritic gout and podagra. Archimataeus, another member of the Salerno school in the twelfth century, wrote

*Gutta in diversis locis nascitur, sed maxime in iuncturis et cubitis, anchis, genibus, et articulis manuum, genuum et pedum, et dicitur gutta quia de humoribus paulatim et guttatim ad partes illas reumatizantibus habet fieri*<sup>8</sup>. (Gout [*gutta*] occurs in various parts of the body but chiefly in the joints, in the elbows, in the hips, in the knees and in the joints of the hands and

1 Hippocrates. The Genuine Works of Hippocrates, translated from the Greek by Francis Adams, New York, W. Wood & Co., 1886.

2 Guainerius, Antonius. De iuncturis sive de arthretica et calculosa passione commentariolus, in Opera Medica, Pavia, Antonius de Carchano, 1481.

3 Lucianus. Podagra tragice, in Sennert,<sup>23</sup> pp. 967-970.

4 Bocking, R., in Acta sanctorum Aprilis, Collecta, digesta, illustrata a Godefrido Henschenio et Daniele Papebrochio e Societate Iesu, Antwerp, apud Michaellem Cnobarum, 1675, book 1.

5 Villehardouin, G. Histoire de l'empire de Constantinople sous les empereurs françois, edited by Charles du Fresne du Cange, Paris, Imprimerie Royale, 1657.

6 Delpeuch, A. La goutte et le rhumatisme, Paris, G. Carre & C. Naud, 1900.

7 Nicolaus Salernitanus. Antidotarium, Pavia, Franciscus de Sancto Petro, 1478-1479.

8 Archimataeus. De instructione medici secundum Archimathaeum, in Collectio salernitana, Naples, publicati a curo di Salvatore de Renzi, 1859, vol. 5, pp. 333-349.

the feet The disease is called gout because it is caused by rheumy humors that flow slowly and drop by drop to the parts mentioned)

For treatment, the author recommended pills containing hermodactyl, i e, *Colchicum autumnale*, or meadow saffron<sup>9</sup>

Thomas Sydenham<sup>10</sup> (1624-1689), whom Trousseau styled "the English Hippocrates,"<sup>11</sup> represents the first milestone that looms high on the crossroads between the old knowledge of gout and the new It was he who recognized gout as a clinical entity and clearly distinguished it from other forms of arthritis and from rheumatism This was, indeed, a remarkable advance that becomes all the more impressive when one realizes that even the celebrated Boerhaave,<sup>12</sup> who died fifty years after Sydenham, failed to make any clear and definite distinction between gout and arthritis

Sydenham gave a colorful and dynamic description of the attack of acute gouty arthritis He said that the fit thunders on the patient usually without warning about 2 o'clock in the morning, seizing the great toe, the heel or the ankle The pain is like that caused by a dislocated bone or the gnawing of a dog and is not relieved by position or warmth The affected part is unable to bear the weight of the clothes on it or the "hard walking in the chamber" The part is swollen and hot, the veins are engorged The complete symptomatic recovery that follows the acute arthritic episode is expressed in these words "Within a few days the other Foot will be in pain as the former was, and if the former has left off aking, the Weakness which rendied it infirm will presently vanish, Strength and perfect Health being so presently restored, as if it never had been out of order"

Such an acute attack of articular gout may last from a few days to a week or more After an asymptomatic interval of weeks, months or, generally, one or more years, the attacks recur involving the same or other joints Such recurrent attacks of acute arthritis appearing suddenly, developing swiftly and disappearing rapidly and completely afford a most valuable clue in the diagnosis of "pre-tophaceous" or presumptive gout One of the reasons that gout remains unrecognized in so many cases is the insistence on the presence of podagra, i e, acute involvement of the metatarsophalangeal joint of the great toe Although this occurs in the majority of the cases in the original attack of the disease, any joint of the foot or other part of the body may be affected at the onset Even in late seizures, which are usually polyarticular, podagra may be absent

Early attacks of gout are usually monarticular, but exceptions are not uncommon, the disease may involve several joints even at the onset Acute attacks of gout with involvement of multiple joints, especially when they occur in younger persons and are accompanied by fever, leukocytosis and an increased sedimentation rate, are often mistaken for rheumatic fever The absence of heart disease, tachycardia and nosebleeds favors the diagnosis of gout Another differential point is the peeling of the skin over affected joints following subsidence of inflammation

9 The use of the word *gutta* goes far beyond the twelfth century Thietmar, Bishop of Merseburg (976-1018), employed it "Fuit olim Godescalki abbatis quidam monachus nomine Aloricus cui in capite suo multum nocuit migraena, aut ex gutta, aut ex vermibus" (Thietmari merseburgensis episcopi chronicon, in Monumenta Germaniae historica, Scriptores rerum Germanicarum, Berlin, 1935, new series, book 9)

10 Sydenham, T The Whole Works of That Excellent Practical Physician, Dr Thomas Sydenham, translated from the Latin by John Pechy, London, R Wellington & E Castle, 1696

11 Trousseau, cited by Llewellyn<sup>37c</sup>

12 Boerhaave, H Aphorisms Concerning the Knowledge and Cure of Diseases, translated from the Latin edition by J Delacoste, London, Innys & Hitch, 1742

This is seen in gout and not in rheumatic fever. Postoperative flare-ups of rheumatic fever appear later<sup>13</sup>, those of gout, earlier<sup>14</sup>.

Other conditions from which acute gouty arthritis has to be differentiated are the following: gonorrheal, acute traumatic, rheumatoid and suppurative arthritis, intermittent hydrarthrosis, acute bursitis and septic cellulitis. The clinical course characteristic of early gouty arthritis, i. e. recurrent attacks and complete symptomatic recoveries, and the prompt favorable response to the early administration of full doses of colchicum should offer no difficulty in establishing the diagnosis of gout. A high concentration of urates in the blood and a family history of gout are additional corroborative diagnostic aids.

Not infrequently acute attacks of gout are provoked by major or minor trauma, operative procedure, overuse of joints, exposure to cold and damp, immoderate drinking, overeating, hunting or fishing expeditions, hiking, treatment at a spa, excessive sexual indulgence, mental strain, emotional stress, ingestion of drugs (mersalyl,<sup>15</sup> epgotamine tartrate,<sup>14</sup> liver extract,<sup>16</sup> gold,<sup>17</sup> dehydrocholic acid<sup>18</sup> and thiamine hydrochloride<sup>19</sup>), purging, severe hemorrhage or transfusion. This should be borne in mind in obtaining the history of a person with acute arthritis. Other conditions often preceding acute gouty attacks are renal colic and olecranal bursitis. The diagnosis of gout should be entertained if, in addition, the history reveals that the attack occurred during the early spring or fall, appeared suddenly in the early morning hours and involved a distant joint (feet, ankles, hands or wrists), especially the great toe. The spine, shoulders and hips are rarely affected. Bald, obese men of ruddy complexion<sup>20</sup> and in the fourth or fifth decade of life are particularly prone to have this disease (gout is uncommon in women and in young persons). A combination of the features described is almost pathognomonic of gout<sup>14</sup>.

The diagnosis of advanced gout is not difficult. After repeated acute seizures for many years, intra-articular structural changes develop and chronic arthritis, with permanent distortion of the joints and occasionally ankylosis, ensues. At this stage there is usually an elevated concentration of urates in the blood, tophaceous deposits of sodium urate crystals are present and frequently punched-out areas of osseous erosion may be revealed in the roentgenograms of the feet and hands. This stage is not reached, however, before ten or twelve years. If one were to wait for the development of these classic changes before making a diagnosis of gout, much valuable time would be lost during which the institution of

13 Ludwig, A. O., Bennett, G. A., and Bauer, W. A Rare Manifestation of Gout Widespread Ankylosis Simulating Rheumatoid Arthritis, *Ann Int Med* **11** 1248-1276 (Jan) 1938

14 Hench, P. S. A Clinic of Some Diseases of Joints, *M Clin North America* **19** 551-583 (Sept) 1935, Comments on the Diagnosis and Management of Gout in Certain Parts of the United States, *Proc Staff Meet, Mayo Clin* **12** 262-269 (April 28) 1937, Diagnosis and Treatment of Gout and Gouty Arthritis, *J A M A* **116** 453-459 (Feb 8) 1941

15 Price, N. L. Gout Following Salyrgan Diuresis, *Lancet* **1** 22-23 (Jan 7) 1939

16 (a) Deitrick, J. E. The Association of Congenital Hemolytic Icterus and Gout, *Internat Clin* **3** 264-277 (Sept) 1940 (b) Opsahl, R. Hematopoiesis and Endogenous Uric Acid, *Acta med Scandinav* **102** 611-628, 1939

17 Pringle, G. L. K. Discussion on the Skin Manifestations in Rheumatism and Gout, *Proc Roy Soc Med* **31** 712-715 (April) 1938

18 Bowers, J. M. Gout, *Northwest Med* **27** 284-288 (Sept) 1938

19 Vorhaus, M. G., and Kramer, M. L. Studies on Thiamin Chloride, *Tr Am Therap Soc* **38** 109-115, 1938

20 Kneel, J., and Haden, R. L. Gout. A Review of Sixty-Two Cases, *M Clin North America* **24** 429-441 (March) 1940

appropriate therapy might result in the postponement of serious renal, cardiovascular and cerebrovascular complications. Gout is more common in the United States than is generally supposed,<sup>21</sup> but unfortunately the disease remains unrecognized for many years. In 40 cases reported from the Mayo Clinic, the average duration was fifteen years.<sup>14</sup>

Sydenham<sup>10</sup> stated the belief that gout was caused by some "morbifick" matter and that the attacks represented nature's way of disposing of the evil substance by removing it into the joints. For this reason he did not approve of attempts to check the acute attack and to curb the natural development of the disease. Boerhaave<sup>12</sup> wrote

Nothing can be more prejudicial in this Disease than to hinder the matter of the Gout from flowing freely to its proper Places. For if the same be retained and hindered, it creates Apoplexies, Palsies and many more wonderful and often suddenly mortal Diseases. They'll not give way unless you bring on a new and smart Fit of the Gout.

Meade<sup>22</sup> expressed this idea in an epigram: "Gout is the only cure of gout." This view goes back to Hippocrates, who taught that organisms are their own physicians. No wonder Emperor Charles V said: "Patience and some crying are the best drugs for gout."<sup>23</sup>

Garrison<sup>24</sup> wrote that Sydenham "stood apart from all medical theorizing and scientific experimentation of his time, disregarded all his predecessors except Hippocrates. He knew nothing of Vesalius, Harvey and Malpighi. His four favorite books were Hippocrates, Cicero, Bacon, and Don Quixote." It seems, however, that another book should be added to Sydenham's library, a book no one ever mentions, much less praises.<sup>6</sup> This excellent volume is called "Tractatus de arthritide,"<sup>23</sup> it was published in 1631, at which time Sydenham was 7 years old. The author was Daniel Sennert (1572-1637), called by his contemporaries a second Galen. Sennert stated the belief that the cause of gout is a morbid humor within the blood vessels resembling the nature of spirits or salts and produced by the liver, spleen and stomach. "Call it bile, pituite, bile mixture, salt, tartar, or whatever pleases you, I consent, provided the thing is well explained," wrote Sennert.

It was not until two hundred years later that more was learned about the "morbifick" matter mentioned by Sydenham, the substance for which Sennert had no name. In 1848, Alfred Baring Garrod<sup>25</sup> reported that the blood of gouty persons contains abnormal quantities of uric acid in the form of sodium urate and that this is due to the inability of the kidneys to excrete uric acid. He expressed the view that gout results from renal insufficiency. Although knowledge regarding the role of the kidneys in gout is still inadequate, it is believed that defective renal function is the result rather than the cause of gout.

Garrod's discovery marks another milestone of overwhelming importance on the road to the newer knowledge of gout. It stimulated extensive research into

21 (a) Cohen, A. Gout, *Am J M Sc* **192** 488-493 (Oct.) 1936, Gout Among Arthritics, *Pennsylvania M J* **41** 1100-1104 (Sept.) 1938. (b) Hench<sup>14</sup> Kinell and Haden<sup>20</sup> Vorhaus and Kramer<sup>19</sup>

22 Meade, cited by Llewellyn<sup>27c</sup>

23 Sennert, D. Opera, Lugduni, Io Antonius Huguetau and Marius Antonius Ravaud, 1666, book 4.

24 Garrison, F. H. An Introduction to the History of Medicine, ed 4, Philadelphia, W. B. Saunders Company, 1929.

25 Garrod, A. B. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease, *Med-Chir Tr*, London **31** 83-97, 1848, The Nature and Treatment of Gout and Rheumatic Gout, London, Watson & Maberly, 1859.

the biochemistry of the disease. However, it is a pity that therewith the problem of gout was transferred from the ward to the laboratory, where it still remains. In 1776, Scheele,<sup>26</sup> a Swedish chemist, demonstrated uric acid in urinary calculi. Twenty-one years later, William Hyde Wollaston<sup>27</sup> analyzed the material obtained from tophi and found that it contained lithic or uric acid. Prior to this, tophi were believed to be made up of chalk and were called chalk stones. This trend of research was brought about by the belief that there is a close relationship between gout and urinary calculi because both conditions often occur simultaneously in the same person. Sydenham,<sup>10</sup> who himself suffered from both diseases, aptly remarks that "gout breeds the stones in very many."

To demonstrate urate in the blood, Garrod<sup>25</sup> devised a simple method known as the "thread experiment." Sodium urate, when present in excess in the blood, will crystallize and adhere to a thread placed in the serum. If the amount of urate is normal, crystals will not form. Some authorities<sup>28</sup> still prefer the crystallographic method of demonstrating blood urates to chemical methods. The normal value for urates determined by the Folin (1930) method varies from 2 to 4.5 mg per hundred cubic centimeters of whole blood. It has been suggested that estimations of urates be carried out on serum derived from blood allowed to clot under oil.<sup>29</sup> With this technique, Jacobson<sup>29</sup> found a serum urate level exceeding 6 mg per hundred cubic centimeters in almost all his gouty patients. The implication appears to be that high values for serum urates are practically always present in established gout.<sup>30</sup> In the experience of others, however, the concentration of blood urates may be normal even in patients with tophaceous gout.<sup>31</sup> Hyperuricemia is infrequent, especially in the early years of the malady. On the other hand, an elevated level of blood urates cannot be considered pathognomonic of gout, because it occurs in a variety of other diseases, such as pneumonia, leukemia, polycythemia, renal insufficiency and acute infections.

The cause of hyperuricemia in gouty subjects is unknown. Increased formation,<sup>32</sup> diminished destruction and deficient excretion of urates have been incriminated. As yet no convincing evidence has been furnished to lend solid support to any of these hypotheses. Destruction of nuclear material, the mother substance of uric acid, is not increased in gout, nor does uricolysis occur in human subjects.<sup>33</sup> Since the observations of Garrod, it has been claimed again and again that the excretion of urates is retarded by some renal condition causing their retention and accumulation in blood, tissues and joints. Points against the renal origin of gout are: 1. Patients with glomerulonephritis and associated hyperuricemia do

26 Scheele, K. W. *Chemical Essays*, translated by T. Beddoes, from the Transactions of the Academy of Sciences at Stockholm, London, J. Murray, 1786, essay IX.

27 Wollaston, W. H. *On Gouty and Urinary Concretions*, *Phil. Tr.* **2**: 386-400, 1797.

28 Weil, M. P. *Considerations sur la goutte aigue, sa frequence, les tests de Garrod, ses formes cliniques, son evolution radiologique*, *Ann. med.-chir.* **4**: 45-53, 1939.

29 Jacobson, B. M. *The Uric Acid in the Serum of the Gouty and of Non-Gouty Individuals. Its Determination by Folin's Recent Method and Its Significance in the Diagnosis of Gout*, *Ann. Int. Med.* **11**: 1277-1295 (Jan.) 1938.

30 Jacobson<sup>29</sup> Ludwig, Bennett and Bauer<sup>13</sup>

31 (a) Gibson, H. J., and Kersley, G. D. *Gout*, *M. Press* **196**: 353-361 (April 27) 1938.  
(b) Kinell and Haden<sup>20</sup>

32 Talbott, J. H., and Coombs, F. S. *Metabolic Studies on Patients with Gout*, *J. A. M. A.* **110**: 1977-1982 (June 11) 1938. Talbott, J. H., Jacobson, B. M., and Oberg, S. A. *The Electrolyte Balance in Acute Gout*, *J. Clin. Investigation* **14**: 411-421 (July) 1935.

33 Thannhauser, S. J. *Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten*, Munich, J. F. Bergmann, 1929. Thannhauser, S. J., and Hemke, W. *Besteht bei Gicht eine funktionelle Störung der Harnsaureausscheidung?* *Klin. Wchnschr.* **2**: 65-67 (Jan. 8) 1923.



not have gout 2 Large numbers of gouty patients do not present evidence of anatomic renal lesions 3 Urates are abundantly excreted at the height of and immediately after acute attacks of gout The possibility of a functional renal disturbance causing an insufficient elimination of urates only has been offered as a reason for the high concentration of urates in the blood and the evolution of gout<sup>33</sup> It has been suggested recently that a functional disturbance of the vegetative nervous system involving renal innervation may have etiologic significance in the disease<sup>34</sup> Another theory is that congenital or acquired difficulty in the elimination of purines because of loss of the power to conjugate them suitably may be the cause of hyperuricemia in gouty patients<sup>35</sup> Recent studies fail to disclose difference in urate clearance in gouty and in nongouty persons<sup>36</sup>

Widespread opinion holds gout to be an expression of disturbed purine metabolism But in gouty patients there is no break or flaw in the chain of intermediary purine metabolism<sup>33</sup> The aminopurines, adenine and guanine, are deaminated to hypoxanthine and xanthine, which, in turn, are oxidized to uric acid Hence, uric acid is regarded as a by-product of normal metabolic processes

According to Garrod,<sup>25</sup> acute attacks of gouty arthritis are caused by precipitation of sodium urate crystals in and around joints However, it does not seem that uric acid is involved in provoking acute attacks At least, the hyperuricemia caused by retention, in acute or chronic nephritis, or by excessive formation of uric acid, as in leukemia, does not invoke attacks of acute arthritis Furthermore, injection of urates into veins or body tissues is painless, such injection does not provoke acute articular exacerbations in a gouty person, nor does it aggravate existing gouty arthritis Finally, the pain in acute gouty arthritis is alleviated by colchicum, which has no action on the urates in the blood or urine

Sennert<sup>23</sup> mentioned in his treatise written three hundred years ago that Julius Alexandrinus knew a gouty person who suffered an acute attack each time he consumed carp Today some physicians<sup>37</sup> envisage gout as an allergic reaction to an exogenous or endogenous allergen The allergen may be derived from food, drink or bacteria or may represent tissue substance which forms after trauma or an operation The purine content of foods and drinks does not seem to play a role As yet there is insufficient evidence to warrant the assumption that food or other allergens are the cause of gout

Tophi are the sole pathologic proof of gout They establish the gouty nature of an associated arthritis Galen<sup>38</sup> (131-200 A D) seems to have been the first to describe them In his opinion, tophi result from a crude humor becoming inspissated and viscous Actually, tophi represent deposits of sodium urate crystals

34 Grabfield, G P A Pharmacologic Study of the Mechanism of Gout, *Ann Int Med* **11** 651-656 (Oct) 1937 Grabfield, G P, and Pratt, J H Action of Cincophen, *J Pharmacol & Exper Therap* **42** 407-439 (Aug) 1931

35 Langdon-Brown, W Gout, M Press **196** 331-334 (April 20) 1938

36 (a) Brøchner-Mortensen, K Uric Acid in Blood and Urine, *Acta med Scandinav* (supp) **84** 1-269, 1937, On Variations in Uric Acid Clearance After Administration of Purine, with Special Reference to the Threshold Problem, *ibid* **99** 525-537, 1939 (b) Coombs, F S, Pecora, L J, Thorogood, E, Consolazio, W V, and Talbott, J H Renal Function in Patients with Gout, *J Clin Investigation* **19** 525-535 (May) 1940

37 (a) Lichtwitz, L Gout, *Bull New York Acad Med* **10** 306-319 (May) 1934 (b) Llewellyn, L J The Etiology of Gout, *New York M J* **118** 601-608 (Nov 21) 1923 (c) Llewellyn, L J, and Beaumont, W M Gout, St Louis, C V Mosby Company, 1921 (d) Gudzent, F Gicht und Rheumatismus, Berlin, Julius Springer, 1928 (e) Widal, F, Abram, P, and Joltrain, E Les cuti-reactions aux vins chez les gouteux, *Presse med* **33** 1425-1426 (Oct 28) 1925

38 Galen, C Opera omnia, editionem curavit Carolus Gottlob Kuhn, Leipzig, Cnobloch 1827, vol 13, book 10

in mesenchymal tissues. The factors involved in the deposition of urates are unknown. Since deposits of sodium urate rarely occur in other conditions with a concomitant hyperuricemia, local factors were incriminated for their development in gout. It was maintained that urate crystals precipitate in traumatized parts of the body and in such parts "as are remotest from the Heart" (such as toe and margin of the ear), and "through which the Liquids flow the most difficultly" (cartilage, tendons and ligaments)<sup>12</sup>. However, the deposition of urates in the tissues cannot be attributed solely to these factors, because blood with a high urate content flows sluggishly in the same parts of the body in conditions other than gout without production of urate deposits. On the other hand, tophi are not uncommon in regions not exposed to trauma.

Tophi most frequently develop in the cartilages of the ears, in olecranal and prepatellar bursae and in and about peripheral joints. They occur less often in the connective tissue of the cutis and subcutis. Sodium urate crystals are often deposited in the interstitial tissue of the kidneys and also in the renal calices and pelves, where they form gravel or calculi<sup>39</sup>. In the joints the urate crystals may invoke changes similar to those prevailing in rheumatoid arthritis and osteoarthritis. Intra-articular tissue reactions as well as periarticular tophi and fibrotic changes may restrict function of the joint and cause unsightly deformities. Tophi are painless, they become painful when they interfere with motion of the joint or during acute exacerbations. Tophi may ulcerate, permitting the stones to peep out like "crab's eyes". Under the microscope, the chalky substance from a broken-down or needled tophus reveals the characteristically needle-shaped and colorless sodium urate crystals. The chemical nature of the "chalk" may also be verified by the murexide test. Microscopic examination and chemical tests are necessary to differentiate true tophi from Heberden's nodes, from calcium deposits, from the nodular swellings occurring in rheumatic fever, rheumatoid arthritis and fibrositis and from gangliomas and sebaceous cysts.

Palpable or visible tophi appear in about 50 per cent of all cases of gout. Infrequent in early gout, they are rather common in advanced gout. Since tophi generally develop eight or ten years after the clinical onset of the disease, one must not hesitate to diagnose presumptive gout in their absence if other evidence present justifies the diagnosis. Sodium urate crystals may be deposited in bone and replace osseous tissue. In roentgenograms, the osseous tophi are revealed as punched-out areas at or near articular margins. Huber,<sup>40</sup> in 1896, was the first to describe the specific roentgenographic features of gout, namely, sharply defined circular or oval areas of diminished density located in the distal ends of the phalanges of the feet and hands. He regarded them as cavities filled with urate crystals.

Roentgen evidence of osseous tophi is seldom discernible in the early years of gout, it was absent even in patients who had had symptoms of the disease for twenty-five or thirty years<sup>20</sup>. Hence, normal roentgenograms do not rule out gout. Moreover, roentgenographic evidence indicative of erosion of bone can also be obtained in various other diseases, a circumstance which further detracts from the value of roentgen examination in gout. Punched-out areas may be seen

39 Urate gravel and stones were called urinary tophi by Hench. However, in gouty persons urate gravel and stones precipitate from urine the urate content of which usually is below the normal level, whereas true tophi precipitate from blood and other body fluids having an increased urate concentration.

40 Huber. Zur Verwerthung der Rontgen-Strahlen im Gebiete der Medicin, Deutsche med Wchnschr. 22 182-184 (March 19) 1896.

in rheumatoid and focal arthritis, osteoarthritis, lupus pernio, cystic disease of the bones, multiple chondiomas and myelomas, Schuller-Christian syndrome, syphilis, tuberculosis and yaws

On the other hand, roentgen examination may furnish valuable information concerning prognosis of surgical treatment for gout. For instance, the bones of hands deformed by chronic arthritis and tophi may have suffered extensive damage. If roentgenography is not resorted to in such cases, the surgical removal of tophi which, instead of the wasted bones, form the supporting frame of the hand, may render wholly useless an efficient though much deformed hand.

The most important milestone in the treatment of gout is the introduction of *Colchicum autumnale*,<sup>41</sup> or meadow saffron, in 1763, by Baron Anton von Storck,<sup>42</sup> physician to the Empress Maria Theresa. Prior to that time, this perennial plant was either unknown in many parts of Europe<sup>43</sup> or was in ill repute possibly because Dioscorides,<sup>44</sup> in the first century A. D., claimed that the plant was poisonous, causing death by suffocation. Baron von Storck,<sup>42</sup> however, demonstrated that small amounts of colchicum can be given with impunity. He stressed the drug's analgesic action for articular pains and its diuretic properties. Quacks were quick to make capital of von Storck's discovery. They flooded the market with "gout specifics"<sup>45</sup> (eau médicinale de Husson, liqueur antigoutteux du Docteur Laville, Reynold's specific, Albert's remedy, Want's medicinal water, etc.), many of which are still on the market and are the choice of some physicians and a large number of persons with gout. Benjamin Franklin is credited with having been the first to introduce colchicum into this country.<sup>46</sup>

Colchicum was known to Byzantine physicians (fifth, sixth and seventh centuries A. D.) under the name of hermodactyl (finger of Hermes).<sup>47</sup> It has also been called *anima articularum* (soul of the joints). A prescription<sup>48</sup> of Jacobus Psychrestus, a Constantinople physician of the fifth century A. D., has been preserved for posterity by the famous Byzantine physician, Alexander of Tralles<sup>48</sup> (525-605 A. D.), who, like Psychrestus and Aetius<sup>49</sup> (sixth century) before him and Paulus Aegineta<sup>50</sup> (625-690 A. D.) after him, employed hermodactyl for painful articular attacks. These early physicians were familiar with the dangerous effects of the drug, they felt that it also had properties other than

41 The name colchicum originates from Colchis, an ancient district of Asia Minor.

42 Storck, A. An Essay on the Use and Effects of the Root of the Colchicum Autumnale, or Meadow Saffron, translated from the Latin, London, T. Becket, & P. A. De Hondt, 1764.

43 Neither hermodactyl nor colchicum is mentioned among more than fifty remedies recommended for the treatment of gout by Nicholas Culpeper in 1681 (The English Physician Enlarged, London, G. Sawbridge, 1681).

44 Dioscorides Anazarbeus (Pedacius). *Arzneimittellehre in fünf Buchern*, translated into German by J. Berendes, Stuttgart, F. Enke, 1902, book 4.

45 Scudamore, C. A Treatise on the Nature and Cure of Gout and Rheumatism, Including General Considerations on Morbid States of the Digestive Organs. Some Remarks on Regimen, and Practical Observations on Gravel, ed. 3, Philadelphia, E. Earle, 1819.

46 Schmitker, M. A. A History of the Treatment of Gout, *Bull. Inst. Hist. Med.* 4: 89-120 (Feb.) 1936.

47 Hermodactyl, 4 scruples, scammony, 2 scruples. To drink with lukewarm water after the patient has been prepared by a good regimen.

48 Alexander (Trallianus). *Medici libri duodecim, Graeci et Latini*. Io Guinterio Andernaco interprete et emendatore. *Adiectae sunt per eundem uariae exemplarium lectionis observationes, cum Jacobi Goupyli castigationibus*, Basel, per Henricum Petrum, 1556.

49 Aetius Amidenus (Antiochemus). *Libri XVI*, Basel, in off. Frobenii 1533-1535, sermo duodecimus.

50 Paulus Aegineta. *Opus de re medica, nunc primum integrum latinitate donatum*, per Joannem Guinterium Andernacum, Paris, apud S. Colinaeum, 1532, book 3.

purgative As yet physicians are unable to explain the striking action of colchicum in the acute gouty attack It does not act as a diuretic, it has no effect on the metabolism of purine bodies, it has no influence on the kidneys, it does not increase excretion of urates or decrease the urate content of the blood Colchicum cannot be regarded as an analgesic, because it fails to influence the pain of a nongouty origin

Colchicum should be administered with great caution or not at all to the old and feeble or to those who suffer from disturbance of the kidneys, heart, liver<sup>51</sup> or gastrointestinal tract Colchicine, the alkaloid and active principle of *Colchicum autumnale*, isolated by Pelletier and Caventou<sup>52</sup> in 1820, is the substance preferred for the treatment of gout because its potency is constant, in contrast to that of the wine and of the tincture of colchicum, which deteriorate on standing A saline purgative such as magnesium sulfate or sodium sulfate ( $\frac{1}{2}$  to 1 ounce [15 to 30 Gm]) should usher in the treatment of an acute attack of gout The treatment is continued, with ingestion of 2 colchicine pills,  $\frac{1}{120}$  gram (0.5 mg) each, followed hourly or every two hours by 1 pill Patients who are being treated for the first time and whose tolerance for colchicine is unknown should be watched carefully It is not necessary to produce nausea or purgation to obtain full therapeutic benefit with colchicine, nausea, vomiting and diarrhea indicate, rather, overdosage, and the administration of the drug should be stopped at once The diarrhea is treated with codeine, camphorated tincture of opium or bismuth subnitrate Patients who are warned by prodromes of an impending attack may prevent or abort it by promptly taking a few colchicine tablets Frequent premonitory symptoms are headache, vertigo, nausea, dyspepsia, gastrointestinal distress, mental depression, nervous irritability, nocturia and euphoria It has been reported recently that gout cycles consisting of suppression of sweating, polyuria and gain in body weight, correlated perhaps with a fall in barometric pressure, may precede acute gouty attacks<sup>52</sup>

Although, in general, colchicine is believed to be highly effective only in the acute gouty attack, there are physicians<sup>53</sup> who advocate its prophylactic use in the asymptomatic periods between attacks One colchicine pill after meals for one week every four weeks,<sup>21a</sup> or for two or three days each week<sup>32</sup> has been recommended It is said<sup>54</sup> that colchicomania develops in patients who take the drug too frequently Such patients become tolerant to the drug, the dose of which must continually be increased for effectiveness Finally, the frequency, severity and duration of the acute attacks increase Personally, I have not encountered untoward effects from the prolonged administration of colchicum

Fifteen centuries elapsed after Jacobus Psychrestus prescribed hermodactyl for his patients in Constantinople before a new milestone was set up in the treatment of gout In 1908, Nicolaier and Dohrn<sup>55</sup> reported that cinchophen (introduced under the proprietary name atophan) increases the urinary output of urate

51 Scheffley, C. H., and Higgins, G. M. The Effect of the Administration of Colchicine After Partial Removal of the Liver, *Proc. Staff Meet., Mayo Clin.* **15**: 536 (Aug. 21) 1940

52 Pelletier, P. J., and Caventou, J. B. Examen chimique de plusieurs végétaux de la famille des colchicées et du principe actif qu'ils renferment, *Ann. de chim. et phys.* **14**: 69, 1820

53 Cohen<sup>21a</sup> Talbott and others<sup>32</sup>

54 Boulin, R. Le colchique et la goutte, *Progrès med.* **67**: 585-588 (April 29) 1939

55 Nicolaier, A., and Dohrn, M. Ueber Wirkung von Chinolincarbonsäuren und ihrer Derivate auf die Ausscheidung von Harnsäure, *Deutsches Arch. f. klin. Med.* **93**: 331-335 (June) 1908

while lowering its level in the blood. In 1911, Weintraud<sup>56</sup> employed the drug in the treatment of gout and found that significant relief followed its use in acute attacks. He stated the belief that the action of cinchophen was more effective than that of colchicum. The exact mechanism of the pharmacologic action is not clear. It has been suggested that cinchophen enhances excretion of urates by direct action on the kidneys<sup>56</sup> or through the nerves controlling renal function,<sup>56</sup> especially through the true sympathetic.<sup>34</sup> Depression of reabsorption of urates by the renal tubular epithelium is another explanation offered.<sup>30b</sup> However, as yet it has not been proved that the uricosuric action of cinchophen is actually responsible for its therapeutic effect in gout. In addition, cinchophen has antipyretic and analgesic properties.

In acute attacks, cinchophen is given for two or three consecutive days in amounts of  $7\frac{1}{2}$  grains (0.48 Gm.) three, four or more times a day. After an interval of from two to four days, administration of the drug may be repeated. To prevent the precipitation of urates as gravel or stones because of the acid reaction of the urine, ingestion of cinchophen should be followed by ingestion of alkaline waters or alkaline powders (potassium citrate, sodium bicarbonate). These render the urine alkaline, in which urates are more soluble. In addition, a liberal intake of fluids and carbohydrates should be insisted on during administration of cinchophen.

It must be kept in mind that cinchophen and its derivatives, such as neo-cinchophen, do not cure gout, furthermore, the relief from pain in acute attacks is not so dramatic and complete as with colchicum. Moreover, cinchophen is known to cause severe and even fatal liver poisoning.<sup>57</sup> When toxic effects develop, such as anorexia, nausea, dyspepsia, gastrointestinal upsets, jaundice, pruritus and urticaria, administration of the drug should be stopped at once. Signs of cinchophen intoxication may first appear long after the administration of the drug was suspended.<sup>57</sup> Because of its toxicity and because there is no safe method of administration, many physicians do not use cinchophen at all. Others<sup>14</sup> feel that the risk from the drug is less than the danger to the patient from the grave renal and vascular complications of gout. Under no circumstances should cinchophen be given uninterruptedly, there should be an intermission of four to five days between courses.<sup>58</sup> The intermittent use of cinchophen is advocated especially in the interparoxysmal periods to avert acute attacks and to prevent or delay the development of complications and of chronic arthritis. In the intervals between acute attacks, cinchophen may be given in doses of 15 grains (1 Gm.) twice a day, one day each week.<sup>58</sup>

From the procession of milestones one point clearly emerges, namely, that gout is still the "physicians' shame," *opprobrium medicorum*, as Daniel Sennert<sup>23</sup> in the sixteenth century put it. Although many theories have been advanced, large in scale and concept, no one as yet even knows the cause of the hyperuricemia present in persons with gout, no one knows the cause of retention of urates by

56 Weintraud, W. Die Behandlung der Gicht mit Phenylchinolincarbonsäure (Atophan) nebst Bemerkungen ueber die diätetische Therapie der Krankheit, *Therap. d. Gegenw.* **13** 97-105 (March) 1911, Weitere klinische Erfahrungen mit Atophan nebst Bemerkungen ueber Gicht und Harnsaure Diathese, *Therap. Monatsh.* **26** 21-29 (Jan.) 1912.

57 Palmer, W. L., and Woodall, P. S. Cinchophen—Is There a Safe Method of Administration? *J. A. M. A.* **107** 760-764 (Sept. 5) 1936. Palmer, W. L., Woodall, P. S., and Wang, K. C. Cinchophen and Toxic Necrosis of Liver. Survey of Problem, *Tr. A. Am. Physicians* **51** 381-393, 1936.

58 Graham, G. Gout, in Price, F. W. A Textbook of the Practice of Medicine, ed. 5, London, Oxford University Press, 1937.

the body tissues and fluids or the cause of the precipitation of sodium urate into the tissues. Since the nature of the basic disturbance of gout is unknown, it is not surprising that as yet no means has been evolved to treat gouty dyscrasia. On the other hand, it seems that perpetual vigilance, adherence to a regimen of hygiene and diet of tried value and wise use of the effective drugs available can to a certain extent alter the clinical course of the disease and retard its progress. However, it appears that, despite the institution of best therapeutic measures, once gout has established itself in a person "the disease sticks to him until death" (Aretaeus, second and third centuries A. D.)<sup>59</sup>

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<sup>59</sup> Aretaeus (Cappadox). *The Extant Works*, edited and translated by Francis Adams, London, The Sydenham Society, 1856.

Recently a new method of approach to the understanding and treatment of gout has been offered. The clinical association of blood dyscrasias and gout prompted Davis (Davis, J. S. *The Liver an Etiological and Therapeutic Factor in Certain Types of Blood Disease and in Gout and Gouty Arthritis*, J. A. M. A. **117** 1648-1649 [Nov. 8] 1941) to assume a possible etiologic connection between gout and a disturbance in hepatic function. He reported gratifying therapeutic results in cases of chronic gouty arthritis and tophaceous gout by injecting a "full complement" liver extract (campolon) which is not heated in preparation and from which purine bodies and proteins are removed.

# Progress in Internal Medicine

## INFECTIOUS DISEASES

### NINTH ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

HOBART A. REIMANN, M.D.

PHILADELPHIA

Judging by the length of this review as compared with the reviews of previous years, and by the number of papers referred to, the war up to now has not greatly interfered with the progress of the study of infectious diseases. Nor has there as yet been as great a change as expected in the trend of interest to problems of infectious diseases in special relation to the war. In the next year or two, however, more change may be anticipated in the quantity and in the nature of published investigations. Evidence of curtailment of medical research is apparent, for example, in the thinness of recent issues of the *Proceedings of the Society of Experimental Biology and Medicine* and in the cancellation of meetings of numerous other scientific societies.

In spite of the war and either as the result of the application of specific and general prophylactic and therapeutic measures or because of a change in the nature of the diseases, the death rates for scarlet fever, whooping cough, diphtheria, influenza, pneumonia, tuberculosis, typhoid fever, appendicitis and puerperal fever in 1942 have reached the lowest levels ever recorded by a large life insurance company<sup>1</sup>. Most striking is the reduction by 55 per cent of the mortality from the various types of pneumonia from 1938 to 1942. In the ten years prior to 1938, the year in which sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was first used, the death rate never fell below 79 per hundred thousand, but by 1942 the rate had dropped to 32 per hundred thousand. According to editorial comment<sup>1a</sup> reviewing the evidence at hand, it is pleasing to learn that there are at present insurmountable difficulties for the successful use of infectious agents as effective weapons of warfare.

### CHEMOTHERAPY

Attempts to discover why the sulfonamide compounds exert a bacteriostatic effect and why certain bacteria are resistant to this effect continue to be made in chemotherapeutic research. In regard to the first problem Davis and Wood<sup>2</sup> point out a correlation between the bacteriostatic power and the protein-binding ability of seven commonly used sulfonamide compounds. The results reported support the current ideas that bacteriostasis depends on specific inhibition of an enzymatic reaction involving paraaminobenzoic acid and that enzymes are protein in nature and inhibition of their action involves some form of chemical interaction between the inhibitor and the enzyme. The authors suggest that the anionic species of the molecule of the sulfonamide compound is the active factor in the mechanism of bacteriostasis.

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From the Jefferson Medical College and Hospital

1 Excellent Health Record of a War Year, Statist. Bull. Metrop. Life Insur. Co. **23** 1-3 (July) 1942

1a Feasibility of Bacterial Warfare, editorial, J. A. M. A. **122** 810-811 (July 17) 1943

2 Davis, B. D., and Wood, W. B. Studies in Antibacterial Action of Sulfonamide Drugs

III Correlation of Drug Activity with Binding to Plasma Proteins, Proc. Soc. Exper. Biol. & Med. **51** 283-285 (Nov.) 1942

An increase in the amount of paraaminobenzoic acid is supposedly one of the chief causes of the resistance to the action of sulfonamide compounds, but this could not be proved until a method was devised by which that substance in cultures of bacteria could be detected and measured. By applying a new technic to cultures of certain staphylococci that were resistant to sulfonamide compounds, Landy and his associates<sup>3</sup> have shown that this was so. At least, the resistant staphylococci make seventy times as much paraaminobenzoic acid in a synthetic medium as do parent drug-sensitive strains of the same bacteria. Drug-fast staphylococci elaborate much more paraaminobenzoic acid than do other varieties of bacteria tested, and evidence suggests that the ability to produce these large amounts is permanent. On the other hand, the resistant strains of *Escherichia coli*, *Vibrio cholerae*, *Salmonella dysenteriae* and *Diplococcus pneumoniae* produced no more demonstrable paraaminobenzoic acid than did their parent drug-sensitive forms. Some other "antisulfonamide metabolite" or proliferative coenzyme may eventually be discovered to account for the resistance of drug-fast bacteria of these varieties to the action of the sulfonamide compounds.

If the suggested factors alone are responsible for the development of resistance to the sulfonamide compounds, it should be possible to overcome them by some means. With this in mind, a group of investigators<sup>4</sup> succeeded in neutralizing the action of paraaminobenzoic acid and of methionine with urea. The addition of urea inhibited the growth of the resistant staphylococci in a concentration of sodium sulfathiazole (sodium salt of 2-[paraaminobenzenesulfonamido]-thiazole), which alone was ineffective, thus overcoming their drug-fastness. It is hoped that this innovation in chemotherapy will prove to be effective clinically. Another way to deal with drug-fast types of bacteria, at least with some of them, is to use penicillin (a filtrate of a broth culture of *Penicillium notatum*), to which they are sensitive. Unfortunately, according to McKee and Houck,<sup>5</sup> pneumococci, staphylococci and hemolytic streptococci may become penicillin fast. In this case, unlike the bacteria resistant to sulfonamide compounds, they lose virulence, according to one report.<sup>6</sup> Their virulence could not be restored by repeated passage in animals.

According to McKinney and Mellon,<sup>7</sup> pneumococci which become resistant to sulfonamide compounds are intermediate variants of the parent drug-sensitive form. The variant forms are not included among the usual M, S and R culture phases, which McLeod several years ago showed to play no part in the matter.

Another chemotherapeutic agent, propamidine (4, 4'-diamidinodiphenoxypropane dihydrochloride), was found to be bacteriostatic for staphylococci.<sup>8</sup> The

3 Landy, M., and Dicken, D. M. A Microbiological Method for the Determination of P-Aminobenzoic Acid, *J Biol Chem* **146** 109-114 (Nov) 1942. Landy, M., Larkum, N. W., Oswald, E. J., and Streightoff, F. Increased Synthesis of P-Aminobenzoic Acid Associated with the Development of Sulfonamide Resistance in *Staphylococcus Aureus*, *Science* **97** 265-267 (March 19) 1943.

4 Tsuchiya, H. M., Tenenberg, D. J., Strakosch, E. A., and Clark, W. G. In Vitro Effect of Urea-Sulfathiazole Combination on Sulfathiazole-Resistant Staphylococci, *Proc Soc Exper Biol & Med* **51** 245-247 (Nov) 1942. Tenenberg, D. J., Tsuchiya, H. M., Clark, W. G., and Strakosch, E. A. In Vitro Effect of Sulfonamides Plus Urea on *Escherichia Coli* in Presence of Para-Aminobenzoic Acid, *ibid* **51** 247-249 (Nov) 1942.

5 McKee, C. M., and Houck, C. L. Induced Penicillin Resistance in a *Pneumococcus* Type III Culture, *Federation Proc* **2** 100 (March 16) 1943.

6 McKee, C. M., and Rake, G. Activity of Penicillin Against Strains of *Pneumococci* Resistant to Sulfonamide Drugs, *Proc Soc Exper Biol & Med* **51** 275-278 (Nov) 1942.

7 McKinney, R. A., and Mellon, R. R. Dissociative Aspects of the Bacteriostatic Action of Sulfonamide Compounds, *J Infect Dis* **68** 233-245 (May-June) 1941.

8 Thrower, W. R., and Valentine, F. C. O. Propamidine in Chronic Wound Sepsis, *Lancet* **1** 133-136 (Jan 30) 1943.



activity of this substance is not inhibited by paraaminobenzoic acid or by pus. It appears to be useful in treatment when applied to superficial infections.

*Chemotherapy in Infections of the Respiratory Tract*—The results of treating 1,635 adults for pneumococcal pneumonia with sulfonamide compounds are reported by Flippin and his co-workers.<sup>9</sup> Sulfadiazine (2-[paraaminobenzene-sulfonamido]-pyrimidine) is at present the drug of choice. The mortality rate for these patients was about 10 per cent, compared with 40 per cent for 1,900 patients with pneumonia in the years just before sulfonamide compounds became available. In the discussion of this report, Rumreich cautions against the indiscriminate use of sulfonamide compounds in treating forms of pneumonia not amenable to chemotherapy. An accurate clinical and bacteriologic diagnosis should be made in each case to guide intelligent therapy. Experiments with a new compound, sulfamethyldiazine (sulfamerizine), are in progress. The drug is as effective as sulfadiazine and is absorbed more rapidly.

Dowling and his associates<sup>10</sup> find that giving only 2 Gm. of sulfadiazine initially and 0.5 Gm. every four hours thereafter, in other words about half the usual amount, is just as satisfactory as far as the mortality rate and the incidence of complications are concerned. However, in those receiving the smaller doses, the duration of the disease was somewhat longer and the incidence of spread to other lobes and of relapse, higher.

Finland<sup>11</sup> reviews information concerning the use of chemotherapy in the treatment of bacteremia. Dick<sup>12</sup> reported recovery in a case of subacute bacterial endocarditis six weeks after the administration of 40 Gm. (1) of sodium sulfadiazine in one dose. Temporary suppression of urine occurred. The patient died a few months later. Others who have tried this enormous dose have not had good results therefrom.

In reference to the unwise use of the sulfonamide compounds for minor infections of the respiratory tract, Spink<sup>13</sup> points out that chemotherapy should not be used for this group of infections except in (1) patients with severe infections actually caused by the hemolytic streptococcus, (2) patients with colds who are known to have cardiac valvular defects, to forestall endocarditis, and (3) obstetric patients who have contracted infection of the respiratory tract at or near term. It is his practice to give sulfadiazine for at least forty-eight hours to every patient having evidence of pneumonia of any kind, but if at the end of that time the cause of the disease is undetermined and if no improvement has occurred, chemotherapy is stopped. I do not agree wholly with this plan, feeling that in the majority of cases of pneumonia one can decide at the outset or soon after whether or not chemotherapy should be used.<sup>14</sup> In the season of 1942-1943, at least, most of the patients with pneumonia whom I observed had the atypical (viral) type, and in only a few cases, in which the diagnosis was doubtful, was chemotherapy used. The mortality among these patients was nil whether treatment was given or not. In a controlled

9 Flippin, H. F., Schwartz, L., and Domm, A. H. Modern Treatment of Pneumococcal Pneumonia, *J. A. M. A.* **121** 230-236 (Jan. 23) 1943.

10 Dowling, H. F., Hartman, C. R., Feldman, H. A., and Jenkins, F. A. The Comparative Value of High and Low Doses of Sulfadiazine in the Treatment of Pneumococcal Pneumonia, *Am. J. M. Sc.* **205** 197-203 (Feb.) 1943.

11 Finland, M. Chemotherapy in the Bacteremias, *Connecticut M. J.* **7** 92-100 (Feb.) 1943.

12 Dick, G. F. Subacute Bacterial Endocarditis: Recovery Following Intravenous Sodium Sulfadiazine, *J. A. M. A.* **120** 24-25 (Sept. 5) 1942.

13 Spink, W. W. The Use and Abuse of Chemotherapy, *Minnesota Med.* **24** 988-990 (Dec.) 1942.

14 Indiscriminate Sulfonamide Therapy in Mild Infections of the Respiratory Tract, editorial, *Pennsylvania M. J.* **46** 719-720 (April) 1943.

study<sup>14a</sup> of 670 cases of infection of the respiratory tract no significant difference was observed in the duration of sickness among those given sulfadiazine as compared with control patients not receiving the drug. Pneumonia occurred equally in both groups. According to Robertson,<sup>15</sup> the possibility of preventing pneumonia with sulfonamide compounds does not seem hopeful in view of the failure of experimental attempts at prevention. In animals, at least, chemotherapy was unexpectedly much less effective if given before than if given after the disease had begun. Furthermore, the low incidence of pneumonia in recent epidemics of mild infection of the respiratory tract does not justify the use of chemoprophylaxis even though physicians had evidence that pneumonia could be prevented by this means. If bacterial pneumonia does occur, it can be satisfactorily treated as it arises. Conditions, however, may change, and then it may be justifiable to use chemoprophylaxis generally. For example, in the event of a large outbreak of influenza or related disease in which secondary bacterial invasion occurs as it did in 1918, there may be no time or opportunity for careful study and selection of cases for treatment.

*Chemotherapy in Other Infections*—Sulfadiazine, because of its low toxicity in comparison with its relatives, is at present the drug of choice in the treatment of hemolytic streptococcal, gonococcal and staphylococcal infections and of various acute bacterial meningitides.<sup>16</sup> In line with current pessimism as to the relative ineffectiveness of chemotherapy for staphylococcal infections, discussed in last year's review,<sup>17</sup> Butler and Valentine<sup>18</sup> state that sulfathiazole is of little value in the treatment of patients with septicemia, and most patients with only a few cocci in their blood recover without it. They believe it should be given nevertheless if visceral involvement occurs, even with light bacteremia. Penicillin may eventually prove to be more useful.

In a study<sup>19</sup> of the value of sulfathiazole in chemoprophylaxis against gonorrhea, the drug was given to a group of Negro soldiers before and after they went on leave. A much larger group of untreated Negroes served as a control. A phenomenal disappearance of gonorrhea and chancroid was reported for the treated group. After chemoprophylaxis the proportion contracting gonorrhea dropped from 171 per thousand to 8 per thousand, and the proportion presenting chancroid from 52 to 6. Admittedly this method seems to be successful, but the risks involved if it is used on a larger scale are as yet unknown. Besides, the profoundly important social implications of such a measure are not mentioned. Serious questions arise as to the frequency of "healthy carriers" in whom symptoms do not occur among persons so treated and as to the possibility under these circumstances of disease being spread even more, to say nothing of the moral effects of the removal of the fear of infection.

14a Rusk, H. A., and van Ravenswaay, A. C. Sulfadiazine in Respiratory Tract Infections. Its Value in Treatment During the Winter of 1942-1943 at Jefferson Barracks, J. A. M. A. **122** 495-496 (June 19) 1943.

15 Robertson, O. H. Newer Knowledge Concerning the Inception of Pneumonia and Its Bearing on Prevention, Ann. Int. Med. **18** 1-14 (Jan.) 1943.

16 Finland, M., Peterson, O. L., and Goodwin, R. A. Sulfadiazine. Further Clinical Studies of Its Efficacy and Toxic Effects in Four Hundred and Sixty Patients, Ann. Int. Med. **17** 920-934 (Dec.) 1942.

17 Reimann, H. A. Infectious Diseases. A Review of Significant Publications in 1941-1942, Arch. Int. Med. **70** 132-177 (July) 1942.

18 Butler, E. C. B., and Valentine, F. C. O. Further Observations on Acute Staphylococcal Infections, Lancet **1** 194-197 (Feb. 13) 1943.

19 Loveless, J. A., and Denton, W. The Oral Use of Sulfathiazole as a Prophylaxis for Gonorrhea, J. A. M. A. **121** 827-828 (March 13) 1943.

In a sort of review of progress in the chemotherapy of tuberculosis, Smith and his associates<sup>20</sup> show that a number of sulfonamide compounds have an inhibiting effect on the growth of tubercle bacilli. The mortality rate in a group of infected animals was reduced from 81 to 44 per cent with promin (a glucoside derivative of 4,4'-diaminophenylsulfone) and to 56 with related drugs. Attempts are being made to produce more effective and less toxic drugs. Another short summary of the problem appears elsewhere,<sup>21</sup> in which it is pointed out that as yet no drugs other than the sulfonamide compounds have been found efficacious in the treatment of tuberculosis in animals or man. Sulfanilamide is of no value in the treatment of leprosy but has proved to be effective in controlling the secondary or complicating infections.<sup>22</sup> Eosinophilia often occurs in lepers treated with sulfanilamide. As to the treatment of leprosy in rats with sulfonamide compounds, conflicting results have been reported. According to Krakower and his associates,<sup>23</sup> sulfanilamide and sulfathiazole were bacteriostatic for a mouse strain of *Mycobacterium leprae*. Growth and dissemination of the lepromas were inhibited while the rats were under treatment, but relapse occurred when therapy was stopped. There was no indication that the bacilli residing in the lesions were killed by the drugs.

A careful analysis of patients with paratyphoid B fever failed to reveal any evidence of the effectiveness of sulfaguanidine in treatment in the acute, the convalescent or the carrier stage.<sup>24</sup> Although sulfadiazine reduced the number of typhoid bacilli in the intestine, the chronic carrier state was not terminated.<sup>24a</sup> The sulfonamide compounds are of no value in the treatment of typhoid fever either.<sup>24b</sup>

According to a report of experience in Africa, sulfapyridine acts as a specific for the bubonic form of plague.<sup>25</sup> Of 547 patients, 345 died. All but 2 of the 131 pneumonic or septicemic patients died. Since most of the patients with the bubonic form who recovered did so by the second or third day, one wonders how much chemotherapy had to do with it, since they were the ones with the mildest infection. Control studies of cases of bubonic plague of similar severity are essential before the value of the drug in the treatment of this disease can be judged.

As in studies reported previously, sulfanilamide had no effect on the "toxic phase" of smallpox, but the later phase, associated with pyogenic bacteria, was modified in some cases.<sup>26</sup>

20 Smith, M. L., Emmart, E. W., and Westfall, B. B. The Action of Certain Sulfonamides, Sulfones and Related Phosphorus Compounds in Experimental Tuberculosis, *J. Pharmacol. & Exper. Therap.* **74** 163-171 (Feb.) 1942.

21 Sulfone Compounds for Pulmonary Tuberculosis, Queries and Minor Notes, *J. A. M. A.* **121** 798 (March 6) 1943.

22 Faget, G. H., Johansen, F. A., and Ross, H. Sulfanilamide in the Treatment of Leprosy, *Pub. Health Rep.* **57** 1892-1899 (Dec. 11) 1942.

23 Krakower, C., Morales-Otero, P., and Antmayer, J. H. The Effect of Sulfanilamide on Experimental Leprosy, *J. Infect. Dis.* **72** 1-10 (Jan.-Feb.) 1943.

24 Scott, T. F. M., Beeson, P. B., and Hawley, W. L. Paratyphoid B Infection. The Ineffectiveness of Sulphaguanidine, *Lancet* **1** 487-490 (April 17) 1943.

24a Hardy, A. V. The Bacteriostatic Action of Sulfadiazine on *E. Typhosa* in Carriers and Cases, *Pub. Health Rep.* **58** 833-839 (May 28) 1943.

24b Hoagland, R. J. The Treatment of Typhoid. The Ineffectiveness of Sulfathiazole and Immune Serum, *J. A. M. A.* **122** 153-156 (July 3) 1943.

25 Plum, D. Plague Epidemic in Nairobi, with Special Reference to Place Incidence and Treatment, *East African M. J.* **19** 3-9 (April) 1942.

26 Wilkinson, P. B. Sulfanilamide in Treatment of Smallpox. Review of One Hundred and Three Cases, *Lancet* **2** 67-68 (July 18) 1942.

After treating 12 patients with nonspecific ulcerative colitis, Kirsner and his collaborators<sup>27</sup> report no beneficial effect from sulfaguanidine (sulfanilyl guanidine). The drug had no advantage over related ones in the treatment of lymphogranuloma venereum of the rectum. The bacterial flora, however, was greatly altered from predominantly coliform to gram-positive bacteria. The change of flora interferes with the normal putrefactive bacteria, helpful in digestion and nutrition, with the result that there was a loss of weight in the test animals. Normal growth may be maintained under these circumstances by the administration of either liver extract or folic acid<sup>28</sup>. Contrary to most reports, as discussed on page 403, the authors<sup>27</sup> noted only slight temporary benefit in 2 cases of infection with *Bacillus dysenteriae* Flexner.

The value of sulfonamide compounds in the therapy of mycotic infections is as yet unknown. Numerous reports of single cases in which recovery took place during therapy are on record but are of little value without controlled observation<sup>29</sup>. Here again the antibiotic agents may be more helpful. Sulfapyridine had no effect on typhus fever in one study,<sup>30</sup> and sulfadiazine failed to control infectious mononucleosis in another<sup>31</sup>. While sulfathiazole and sulfapyridine had no effect on the protozoan *Toxoplasma* in vitro, they completely inhibited its growth in infected mice when given orally<sup>32</sup>. In most other infections the reverse usually occurs.

From the first comprehensive study to ascertain how many people actually have died from the effects of sulfonamide compounds, Sutliff and his associates<sup>33</sup> conclude that the small number of such persons warrants the continued use of the drugs in the usual dosages for the diseases in which they are of value. The benefits derived outweigh the risk involved. They encountered the usual difficulties in their search because of the incomplete or unsatisfactory records of many cases. For example, only one death ascribed to a sulfonamide compound appeared to have been noted among 685 deaths in cases of pneumonia in New York, but a more careful perusal of the statistics showed that the one death from toxicity occurred among 161. As near as one can judge, 1 death is caused by a sulfonamide compound in every 1,600 cases of pneumonia in which such drugs are used. It is often difficult and at times impossible to judge whether death is caused by the treatment, by the disease or by the combination of the two.

In discussing this paper, Long estimates that about 1,700 tons of sulfonamide compounds were made in the United States in 1941 and that between 10,000,000 and 15,000,000 persons received them in some form of therapy. He points out the need for using these drugs only when they are indicated, because of the possible sensitization of a large percentage of persons who take them.

27 Kirsner, J. B., Rodaniche, E. C., and Palmer, W. L. Use of Sulfaguanidine in Non-Specific Ulcerative Colitis and Other Infections of the Bowel, *Am J Digest Dis* **9** 229-233 (July) 1942.

28 Gant, O. K., Ransone, B., McCoy, E., and Elvehjem, C. A. Intestinal Flora of Rats on Purified Diets Containing Sulfonamides, *Proc Soc Exper Biol & Med* **52** 276-279 (April) 1943.

29 Marshall, M., and Teed, R. W. *Torula Histolytica* Meningoencephalitis. Recovery Following Bilateral Mastoidectomy and Sulfonamide Therapy, Preliminary Report, *J A M A* **120**:527-529 (Oct 17) 1942.

30 Donald, C., and Barker, P. B. Louse-Borne Typhus Fever, *Brit M J* **2** 333-335 (Sept 19) 1942.

31 Kilham, L., and Steigman, A. J. Infectious Mononucleosis, *Lancet* **2** 452-454 (Oct 17) 1942.

32 Sabin, A. B., and Warren, J. Therapeutic Effectiveness of Certain Sulfonamides on Infection by an Intracellular Protozoan (*Toxoplasma*), *Proc Soc Exper Biol & Med* **51** 19-23 (Oct) 1942.

33 Sutliff, W. D., Helpern, M., Griffin, G., and Brown, H. Sulfonamide Toxicity as a Cause of Death in New York City in 1941, *J A M A* **121** 307-312 (Jan 30) 1943.

*Penicillin*—Encouraging results are accruing from clinical studies on the use of penicillin in treating infections. The substance as developed by British investigators is said to have several advantages over sulfonamide compounds. It is relatively nontoxic, nonhemolytic and highly soluble, and its action is not inhibited by pus or by paraaminobenzoic acid. A form of penicillin called penicillin B was recently discovered<sup>34</sup>. In addition to being active against gram-positive cocci, it attacks gram-negative ones as well, but it is also toxic for mice. Another compound consisting of esters of the acid of penicillin was studied by Meyer and his co-workers<sup>35</sup>.

Thus far in clinical use penicillin seems to be effective for infections with staphylococci, hemolytic streptococci, certain susceptible strains of pneumococci and gonococci<sup>35a</sup>. Unfortunately, thus far it has been of no value in the treatment of the subacute bacterial endocarditis due to *Streptococcus viridans*. The substance is best given intravenously in physiologic solution of sodium chloride by the continuous drip method in doses of 30,000 to 40,000 Florey, or Oxford, units a day. In 7 patients with various severe infections so treated Herrell<sup>36</sup> reports good results and no toxic effects, but unfortunately controls in a study like this are difficult to arrange. Penicillin was effective in treating several patients infected with gonococci which were resistant to sulfonamide compounds<sup>37</sup>. In my own experience, recovery occurred in a case of severe primary staphylococcal pneumonia in which 440,000 units of penicillin was given over a period of thirteen days. Penicillin was found to be effective against both pneumococci that were resistant and pneumococci that were susceptible to the action of sulfonamide compounds<sup>38</sup>. It must be recalled here that pneumococci may become penicillin fast. Penicillin-fast pneumococci are not resistant to sulfonamide compounds. One wonders whether a given strain of pneumococci may become resistant to both penicillin and a sulfonamide compound. In the experience of Schmidt and Sesler<sup>39</sup> pneumococci which become penicillin resistant retain their virulence, in contrast with the observations discussed previously. The versatility of the pneumococcus in adapting itself specifically to such diverse agents as bile, the sulfonamide compounds, penicillin and ethylhydrocupreine hydrochloride is remarkable.

By using a protamine it is possible to "sensitize" gram-negative bacteria, ordinarily not susceptible, to the action of gramicidin<sup>40</sup> (a crystalline substance

34 Roberts, E. C., Cain, C. K., Muir, R. D., Reithel, F. J., Gaby, W. L., Van Bruggen, J. T., Homan, D. M., Katzman, P. A., Jones, L. R., and Doisy, E. A. Penicillin B, an Antibacterial Substance from *Penicillium Notatum*, *J. Biol. Chem.* **147**: 47-58 (Jan.) 1943.

35 Meyer, K., Hobby, G., and Chaffee, E. On Esters of Penicillin, *Science* **97**: 205-206 (Feb. 26) 1943. Meyer, K., Hobby, G. L., and Dawson, M. H. The Chemotherapeutic Effect of Esters of Penicillin, *Proc. Soc. Exper. Biol. & Med.* **53**: 100-104 (June) 1943.

35a Florey, M. E., and Florey, H. W. General and Local Administration of Penicillin, *Lancet* **1**: 387-396 (March 27) 1943. Blake, F. G., and Craige, B. Penicillin in Suppurative Disease of the Lungs. Report of Three Cases, *Yale J. Biol. & Med.* **15**: 507-516 (Jan.) 1943.

36 Herrell, W. E. Further Observations on the Clinical Use of Penicillin, *Proc. Staff Meet., Mayo Clin.* **18**: 65-76 (March 10) 1943.

37 Herrell, W. E., Cook, E. N., and Thompson, L. Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, *J. A. M. A.* **122**: 289-292 (May 29) 1943.

38 Tillett, W. S., Cambier, M. J., and Harris, W. H. Sulfonamide-Fast Pneumococci. A Clinical Report of Two Cases of Pneumonia Together with Experimental Studies on the Effectiveness of Penicillin and Tyrothricin Against Sulfonamide-Resistant Strains, *J. Clin. Investigation* **22**: 249-255 (March) 1943.

39 Schmidt, L. H., and Sesler, C. L. Development of Resistance to Penicillin by Pneumococci, *Proc. Soc. Exper. Biol. & Med.* **52**: 353-357 (April) 1943.

40 Miller, B. F., Abrams, R., Dorfman, A., and Klein, M. Antibacterial Properties of Protamine and Histone, *Science* **96**: 428-436 (Nov. 6) 1942.

isolated from soil bacilli, highly bactericidal for gram-positive micro-organisms) Methylthionine chloride and acriflavine have a similar effect in increasing the effectiveness of tyrothricin (an extract from *Bacillus brevis* of Dubos) It appears that other compounds, such as histone, with a relatively simple polypeptide configuration may also be found to have antibacterial properties Protamine and histone are too toxic for therapeutic use

In Neter's <sup>41a</sup> experiments both pyocyanase and zephiran (a mixture of alkyl, dimethyl and benzyl ammonium chlorides) detoxified tetanus toxin Zephiran also delays the clotting of oxalated plasma by staphylococci and inhibits fibrinolysis by *Streptococcus haemolyticus* Zephiran chloride has recently been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for listing in "New and Non-Official Remedies" <sup>41b</sup> It is a new disinfectant, germicidal for many pathogenic nonsporulating bacteria and fungi Solutions of the substance have low surface tension and have detergent, keratolytic and emulsifying action In dilutions of 1:1,000 to 1:10,000 it is used to disinfect the surface of skin and mucous membranes

Other antibiotic substances, such as pyocyanine, synthetic hemipyocyanine and pyocyanase, have been tested <sup>42</sup> Both tyrothricin and hemipyocyanine are fungistatic and may be of value in the treatment of fungous infections

#### COCCID DISEASES

*Pneumococcic Pneumonia*—The death rate from pneumonia of all types in 1941-1942 decreased to the lowest rate ever recorded by a large life insurance company, <sup>43</sup> dropping successively from 44, 40 and 32 per hundred thousand in the past three years The decline is not wholly due to the use of sulfonamide compounds since it had been slowly progressing for many years before and is influenced by other factors as well, but chemotherapy, introduced in 1938, almost certainly caused a sharper decline I believed that the death rate would be even lower this year because of the great number of cases in which the pneumonia was of a benign atypical ("viral") type, but statistics show otherwise Apparently the death rate has increased by 40 per cent over a similar period in 1943, supposedly because of fatal cases of "viral" pneumonia <sup>44</sup> This is surprising since in practically all reports of series of cases of "viral" pneumonia the mortality rate is nil Deaths said to be due to "viral" pneumonia call for reinvestigation

According to a survey <sup>45</sup> of over 30,000 cases of pneumonia in the years 1938 to 1940, over three fourths were caused by pneumococci The proportion was

41 (a) Neter, E Effect of Alkyl-Dimethyl-Benzyl-Ammonium Chlorides (Zephiran) upon Tetanus Toxin, *Proc Soc Exper Biol & Med* **51** 254-256 (Nov) 1942, Effects of Alkyl-Dimethyl-Benzyl-Ammonium Chlorides upon Plasma Coagulation by *Staphylococcus* and Fibrinolysis by *Streptococcus*, *ibid* **51** 256-258 (Nov) 1942 (b) New and Nonofficial Remedies, *J A M A* **120** 289 (Sept 26) 1942

42 Stokes, J L, Pick, R L, and Woodward, C R, Jr Antimicrobial Action of Pyocyanine, Hemipyocyanine, Pyocyanase and Tyrothricin, *Proc Soc Exper Biol & Med* **51** 126-130 (Oct) 1942

43 Pneumonia Death Rate Lowest on Record, *Statist Bull Metrop Life Ins Co* **23** 8-10 (Nov) 1942

44 Recent Increase in Pneumonia Mortality, *Statist Bull Metrop Life Insur Co* **24** 7-9 (April) 1943

45 Rumreich, A S, Shaughnessy, H J, Mulcahy, J V, Willett, J C, Kellogg, W H, and Mitchell, W C A Nation-Wide Study of the Bacterial Etiology of the Pneumonias, *Pub Health Rep* **58** 121-135 (Jan 22) 1943

reversed in 1942 in many localities where atypical ("viral") pneumonia was common. The distribution of cases according to type of pneumococci remained constant in each area investigated from year to year. In the two year period the predominant types were prevalent in the following order: I, III, VII, VIII, IV, VI, V, XIX and XIV. These types caused 75 per cent of all cases of pneumococcic pneumonia in which the type was determined. In a survey<sup>46</sup> of an urban population in the years 1934 to 1936 the incidence of pneumonia of all types was 5.4 per thousand persons, the average duration of disability was thirty-nine days and the case fatality rate was 17.5 per cent.

Finland<sup>47</sup> reviews the epidemiology of pneumococcic infection. It is clear from modern bacteriologic studies that both patients with pneumonia and carriers of pneumococci are responsible for the spread of this disease, but carriers, being more numerous, are probably the more important source of infection. The spread of disease-producing pneumococci is greatest within households, barracks or dormitories, where intimate and prolonged personal contact is favored. Although there is reason to believe that infection is usually airborne, there is, strangely enough, but little evidence to prove that it is. The problem is discussed again on page 398. Because of the knowledge now available, it is important to determine the type of the infecting pneumococci in each case whether the disease produced is pneumonia or otherwise. Each patient must be regarded as a disseminator of infection and isolated from others. Sputum, saliva, handkerchiefs, bed clothing and other articles that are likely to harbor pneumococci should be sterilized. Dusting should be carefully done.

It seems to me that the influence of mild acute infections of the respiratory tract as a precursor of pneumonia is not adequately stressed in the review. Since such infections precede from 50 to 80 per cent of cases of pneumococcic pneumonia, their prevention would seem to be the greatest single factor in controlling the incidence of pneumonia. It is generally believed that a person's liability to contract pneumococcic infection is dependent on his susceptibility to, or resistance against, the pneumococcus, and if resistance could be kept intact by preventing "colds," pneumococcic invasion and disease would not occur in many persons.

Finland<sup>48</sup> discusses the use of antipneumococcic serums for pneumonia caused by the higher-numbered types of pneumococci. There are now 68 recognized types and subtypes, which seems to complicate the matter greatly, but the difficulties are lessened if the antiserums are made with given types and their subtypes. In general such antiserums are just as valuable in treatment as those for the lower-numbered types if given with the same precision, and, like them, are particularly valuable for patients who are sensitive to sulfonamide compounds or for those who are infected with pneumococci that are resistant to these compounds. Because the distribution of the higher-numbered types is the same in healthy carriers as in patients with pneumonia, it is often difficult to decide whether the pneumococci found in the sputum are the cause of the pneumonia or merely reside as saprophytes in the nasopharynx. When pneumococci are present in the blood or the spinal fluid, they are almost certainly the cause of the disease. Invasiveness of the relatively less

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46 Britten, R. H. The Incidence of Pneumonia as Recorded in the National Health Survey, *Pub. Health Rep.* **57** 1479-1494 (Oct 2) 1942.

47 Finland, M. Recent Advances in the Epidemiology of Pneumococcal Infection, *Medicine* **21** 307-344 (Sept.) 1942.

48 Finland, M. The Present Status of the Higher Types of Antipneumococcus Serums, *J. A. M. A.* **120** 1294-1307 (Dec 19) 1942.



virulent higher-numbered types of pneumococci depends largely on lack of resistance in the host

Faller and his associates<sup>49</sup> point out how unreliable statistics of pneumonia may be, even in hospital practice. In scrutinizing the records of 377 deaths ascribed to pneumonia, this disease was obviously the primary cause of death in only 35 per cent of the cases and probably not the cause in another 8 per cent. In 19 per cent there was no evidence in the records by which pneumonia could be diagnosed at all. How can one account for such a high proportion of errors? Some of the factors, according to the authors, are as follows: (1) There is a tendency to use the term "pneumonia" to satisfy legal requirements when a named cause of death is needed in an obscure case, (2) many physicians diagnose pneumonia too readily merely because of fever and pulmonary rales, (3) conditions such as pulmonary collapse or infarct are often misdiagnosed, especially in surgical cases, (4) there is often uncertainty as to whether the patient died from pneumonia or whether pneumonia developed because the patient was dying, (5) records are often poorly kept, and nomenclature is confused, (6) roentgenograms were made in only 38 per cent of cases, possibly, to cite one reason at least, because of the exorbitant charges often made for this service, and (7) attempts to discover the cause of the pneumonia bacteriologically were made in only 15 per cent of cases. The last shortcoming is most discouraging to those who have made efforts to stimulate interest in etiologic diagnosis by which accurate clinical diagnosis and rational specific therapy is guided.

Frisch and his co-workers<sup>50</sup> give a summary of their work concerning the value of examining sputum stained by Wright's method as a guide to prognosis and therapy in a number of similar papers in different journals. In general, regardless of the type of pneumococcus except type III, of the duration of disease before specific therapy is begun or of the presence of bacteremia, the prognosis is good and the mortality rate is 2 per cent when not more than 10 pneumococci per field are present. With 11 to 30 per field the mortality rate is 9 per cent, with 31 to 75, 30 per cent, and with a number exceeding 75 per field, 77 per cent. Chemotherapy had no appreciable effect on the fatality rate when the count was high. Antiserum in adequate doses causes prompt clumping of pneumococci in the sputum, while the sulfonamide compounds reduce the numbers present within twelve to thirty-six hours unless the pneumococci are drug resistant. Matters are different when pneumonia is caused by type III pneumococcus because of the large amount of capsular polysaccharide made by this bacterium. In stained smears of sputum, the polysaccharide appears as a reticulum. When "reticulation" is present, the mortality rate is 79 per cent, compared with 7 per cent when it is absent. In patients with "reticulated" sputum sulfathiazole lowered the mortality rate from 100 to 67 per cent. Antiserum is of no avail and should not be used unless the pneumococci are drug resistant.

Frisch's test, while valuable, serves as an indication among others of the prognosis and as a guide to therapy. It cannot be applied, of course, in the occasional

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49 Faller, C. P., Quickel, K. E., and Smith, C. W. All That Is Called Pneumonia Is Not Pneumonia. A Critical Analysis of Three Hundred and Seventy-Seven Deaths Ascribed to Pneumonia Occurring in Hospitals in Central Pennsylvania, *Pennsylvania M. J.* **46** 339-345 (Jan.) 1943.

50 Frisch, A. W., Price, A. E., and Myers, G. B. Pneumococcal Pneumonia. The Prognostic Significance of the Number of Pneumococci in the Sputum in Relation to Therapy, Bacteremia, Type, Leukocyte Count, Duration of the Disease, Age and Degree of Involvement, *J. Clin. Investigation* **22** 207-214 (March) 1943, Type III Pneumonia. The Prognostic Significance of Reticulation in Relation to the Number of Pneumococci in the Sputum, Therapy, Bacteremia, Leukocyte Count, Age and Degree of Involvement, *ibid.* **22** 215-220 (March) 1943.



case in which sputum is not raised, and it is unreliable if other complicating factors are present

Robertson<sup>16</sup> summarizes his work on the genesis of pneumonia. Certain conditions are essential to cause the disease: (a) the implantation of pneumococci in the terminal airways either by inhalation or by aspiration of infected fluid, (b) the presence of a viscous medium, which prevents their rapid expulsion from this region of the lung, and (c) local irritation such as may be caused by mild infection of the respiratory tract. The escape of infected fluid exudate from the upper respiratory tract past the epiglottis plays a much more important role in the inception of pneumonia than does the inhalation of bacteria-laden droplets. The spread of infection within the lungs is brought about by the migration of infected thin edema fluid.

In discussing the cause of postoperative pneumonia Robertson refers to the work of Nungester and Klepser, who show how important closure of the epiglottis is in preventing aspiration of fluid. Atelectasis is also a factor in hindering the expulsion of exudate and favoring pneumonia. Pneumonia is particularly liable to occur if there is mild infection of the respiratory tract to provide the factor of irritation. Irritation, therefore, is a more decisive factor than obstruction in determining the inception of pneumonia.

Nungester and his associates<sup>51</sup> show that in addition to the presence of viscous material in the lungs to favor the development of pneumonia, the relative force of inspiration and expiration is also important in determining whether mucus is aspirated or expelled.

An interesting experiment was made by linking fluorescein isocyanate to the antibody of type III pneumococcus.<sup>52</sup> The antibody conjugate could be specifically stained in localized areas in mice infected with type III pneumococcus. The method seems to be a valuable one to demonstrate antigens in tissues, especially in investigations to determine the damage supposedly resulting from union of antigen and antibody, and perhaps in locating the sites of certain viruses.

Another unexpected antigenic relationship of pneumococci to unrelated bacilli was described in two papers.<sup>53</sup> Several years ago a relationship between type II pneumococci and type B Friedlander bacilli was discovered, now one learns that type VI and type XXIX pneumococci and type B *Haemophilus influenzae* have certain capsular antigens in common.

*Other Bacterial Pneumonias*—Studies on the clinical and pathologic aspects of staphylococcic pneumonia have been published.<sup>54</sup> Staphylococcic pneumonia may develop in patients with influenza and may assume epidemic proportions in local areas during an epidemic of influenza. It assumes various forms and has various sequels.

51 Nungester, W. J., Klepser, R. G., and Kempf, A. H. Consideration of the Respiratory Pattern as a Predisposing Factor in the Etiology of Pneumonia, *J. Infect. Dis.* **71** 57-60 (July-Aug.) 1942.

52 Coons, A. H., Creech, H. J., Jones, R. N., and Berliner, E. The Demonstration of Pneumococcal Antigen in Tissues by the Use of Fluorescent Antibody, *J. Immunol.* **45** 159-170 (Nov.) 1942.

53 Neter, E. Antigenic Relationship Between *H. Influenzae* Type B and *Pneumococcus* Type VI, *Proc. Soc. Exper. Biol. & Med.* **52** 289-292 (April) 1943. Zepp, H. D., and Hodes, H. L. Antigenic Relation of Type B *H. Influenzae* to Type 29 and Type 6 *Pneumococci*, *ibid.* **52** 315-317 (April) 1943.

54 Finland, M., Peterson, O. L., and Strauss, E. Staphylococcic Pneumonia Occurring During an Epidemic of Influenza, *Arch. Int. Med.* **70** 183-205 (Aug.) 1942. Wollenman, O. J., and Finland, M. Pathology of Staphylococcal Pneumonia Complicating Clinical Influenza, *Am. J. Path.* **19** 23-41 (Jan.) 1943.

A case of pneumonia caused by *Micrococcus tetragenus* is reported<sup>55</sup> A case of pneumonia was reported in which *Trichomonas buccalis* was thought to be the cause, but evidence therefor is doubtful<sup>56</sup> The mere presence of certain microorganisms does not always indicate a causal relationship to disease The same criticism may be applied to the alleged causative relation of *Streptococcus viridans* to cases of pneumonia<sup>56a</sup>

*Pneumococcic Meningitis*—Hodes Smith and Ickes<sup>57</sup> report their results in treating patients for pneumococcic meningitis Of 60 patients, recovery occurred in 42 per cent after treatment with sulfapyridine, sulfadiazine or sulfathiazole Sixty-four per cent of patients over the age of 2 recovered This percentage is much higher than that obtained by others Twenty-nine patients received specific serum in addition, but the authors were unable to say that those who received it were aided more than those treated by chemotherapy alone

*Streptococci*—An interesting point of view in regard to infection with hemolytic streptococci is proposed by Boisvert and his associates<sup>58</sup> Streptococcic infection, they believe, may be compared with tuberculosis to advantage, and the term "streptococcosis" introduced to embrace it In both conditions, first infections and reinfections have similar characteristic peculiarities In early infancy, for example, hemolytic streptococcic infection behaves as a subacute disease, often lasting six weeks, which may be regarded as a clinical entity called "streptococcic fever, childhood type" In later life, reinfection is more apt to cause short violent local disease like acute tonsillitis, which may be called "streptococcic fever, adult type" Scarlet fever may be a manifestation of a special allergic condition in a child who had previously had streptococcic fever

Further analogy with tuberculosis is suggested by the carrier or latent state, designated "latent streptococcosis" A study of the records of nearly 5,000 children at the New Haven Hospital indicates that 14 per cent had "streptococcosis" and that in 25 per cent hemolytic streptococci were present in the nose, throat or elsewhere as "latent streptococcosis" In studying the authors' concept one wonders whether or not their plan may not be generalized and applied to other infectious diseases, such as those caused by pneumococci and staphylococci and perhaps those caused by certain filtrable viruses as well

An explosive outbreak of hemolytic streptococcus sore throat occurred in a military camp in June 1942<sup>59</sup> Ten per cent of 3,000 men were sick The disease seemed to be caused by massive inoculation originating from a common source, since there was no evidence of spread from person to person The epidemic affected nearly 200 soldiers during the first two days, after which it rapidly disappeared Although the disease was disabling, it was seldom grave and seemed to be caused by massive infection with hemolytic streptococci of type 15, group A, rather than with a particularly virulent strain There were few complications, but a scarlatinal rash occurred in 25 The severity was not different in those with or without

55 Tobin, W R Pneumonia Caused by *Micrococcus Tetragenus*, J A M A **121** 41 (Jan 2) 1943

56 Glaubach, N, and Guller, E J Pneumonia Apparently Due to *Trichomonas Buccalis*, J A M A **120** 280-281 (Sept 26) 1942

56a Solomon, S, and Kalkstem, M Pneumonia Due to the *Streptococcus Viridans*, Am J M Sc **205** 766-770 (June) 1943

57 Hodes, H L, Smith, M H D, and Ickes, H J Sixty Cases of Pneumococcic Meningitis Treated with Sulfonamides, J A M A **121** 1334-1337 (April 24) 1943

58 Boisvert, P L, Darrow, D C, Powers, G F and Trask, J D Streptococcosis in Children A Nosographic and Statistical Study, Am J Dis Child **64** 516-534 (Sept) 1942

59 Bloomfield, A L, and Rantz, L A An Outbreak of Streptococcic Sore Throat in a Camp J A M A **121** 315-319 (Jan 30) 1943

exanthem In no case did rheumatic fever or nephritis occur as a sequel In incidental discussion the authors again raise the point as to whether hemolytic streptococcus tonsillitis and scarlet fever should be considered as separate diseases or not They favor the view, as do many others, of regarding them as one disease with different manifestations but subject to the same rules of quarantine

Extensive research in streptococcal infection was made by Rantz and his co-workers In one report<sup>60</sup> they state that, of 392 strains of streptococci from all human sources except the respiratory tract, only 6.6 per cent belonged to group A and only 28 per cent were beta hemolytic, the remainder were of the viridans or nonhemolytic variety Group A hemolytic streptococci therefore are seldom present anywhere except in the respiratory tract Of the 392 strains, 82 per cent could be assigned to one of the Lancefield groups A, B, C, D, F, G and H The majority were of group D, which are exceedingly resistant to the action of the sulfonamide compounds

Hemolytic streptococci other than those of group A may cause severe infection in man<sup>61</sup> Of 13 cases of septicemia, 6 were due to such organisms—4 to those of group B, 1 to those of group C and 1 to those of group D Sulfanilamide was useful against each group except D It is obvious that it is desirable to determine the group and the type number of all hemolytic streptococci causing infections as a guide to therapy and prognosis

The value of each of various tests used for the determination of infection with the hemolytic streptococcus was briefly discussed<sup>62</sup> The authors applied the slide agglutination method for types 1, 2, 4, 6, 9, 11, 12, 13 and 25 to the serums of 47 normal persons and compared the results with the antitoxic immunity by means of the antistreptolysin measurement Almost one half of these persons had agglutinins for one or more types in a titer of 1:4 or less, and these had not had previous known infections with *Str. haemolyticus* However, for 47 per cent of those who had had such infections the titer was 1:4 and in some cases as high as 1:8 No correlation was found between the amounts of circulating agglutinins and the amount of antistreptolysin Among 24 patients with scarlet fever, agglutinins were demonstrated in only about one half Agglutinins for heterologous types also developed occasionally In 2 cases agglutinins were present at the onset of the disease, indicating that they in themselves do not confer immunity Similar studies are in progress to determine whether the slide agglutination test will be of value in the diagnosis of rheumatic arthritis and rheumatic fever, but the authors are doubtful of its value because of the presence of antibodies in so many normal persons

Enterococci, a group of hemolytic and nonhemolytic streptococci of Lancefield's group D, are isolated from human sources<sup>63</sup> other than the respiratory tract more frequently than any other streptococci They are of low invasiveness but may be the cause of otitis media, endocarditis, peritonitis and infections of the urinary

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60 Rantz, L. A. The Serological and Biological Classification of Hemolytic and Non-hemolytic Streptococci from Human Sources, *J. Infect. Dis.* **71** 61-68 (July-Aug.) 1942

61 Rantz, L. A., and Kirby, W. M. M. Hemolytic Streptococcus Bacteremia. Report of Thirteen Cases with Special Reference to Serologic Groups of Etiologic Organisms, *New England J. Med.* **227** 730-733 (Nov. 12) 1942

62 Rantz, L. A., Kirby, W. M. M., and Jacobs, A. H. Group A Hemolytic Streptococcus Antibodies. I. Griffith Type Agglutinin and Antistreptolysin Titers in Normal Men and in Acute Infections, *J. Clin. Investigation* **22** 411-418 (May) 1943

63 Rantz, L. A., and Kirby, W. M. M. Enterococcal Infections. An Evaluation of the Importance of Fecal Streptococci and Related Organisms in the Causation of Human Disease, *Arch. Int. Med.* **71** 516-528 (April) 1943

tract They are exceedingly resistant to the bacteriostatic effects of sulfonamide compounds

In another study<sup>64</sup> tests were performed on children before and after tonsillectomy Children who were carriers of *Str haemolyticus* were found to have an increased amount of antibody When the carrier state was terminated by tonsillectomy, there was a constant decline in the titer of antistreptolysin within sixty days, but no consistent fall in the titer of agglutinin Any interpretation of these results should not be oversimplified and should not be used to support the practice of routine removal of tonsils It is probable that hemolytic streptococci may be harbored in lymphoid tissue in the respiratory tract other than the tonsils

In a review of the subject of focal infection as it pertains to ophthalmology Woods<sup>65</sup> has come to the conclusion that the removal of minor and symptomless foci of infection as a cure-all for endogenous ocular disease has no place in modern practice

Rhoads and Afremow<sup>66</sup> found hemolytic streptococci to be the cause of two thirds of the attacks of tonsillitis, pharyngitis, laryngitis and sinusitis in young adults Persons who carry hemolytic streptococci in their throats or green-forming streptococci in their noses usually have active infection or are convalescent from active infection Twenty per cent of a group of students were found to be carriers of *Str haemolyticus* Green-forming cocci, including both streptococci and pneumococci, were found in all cultures of secretions from throats and are therefore regarded as normal inhabitants of the pharynx Carriers of hemolytic streptococci are potential sources of infection for others and perhaps ought to be quarantined Methods such as the administration of sulfanilamide, the application of ultraviolet rays or the spraying of the throat with a solution of tyrothricin had no effect in ridding carriers of their streptococci Spraying the throat with a solution of sodium sulfathiazole was effective in some cases

In the experience of Colebrook and his co-workers<sup>67</sup> nonhemolytic streptococci were cultured from 13 patients suffering from a disease like that caused by group A hemolytic streptococci All 13 strains reacted specifically in group A antiserum, and 11 were agglutinated by type XII antiserum The infections caused by these 11 strains developed shortly after infections with type XII hemolytic streptococci had occurred in the wards Both the hemolytic and the nonhemolytic type XII strains were insensitive to sulfanilamide These observations indeed seem to add confusion and uncertainty to identifications by grouping and typing and raise the old question of the relationship between the hemolytic and the nonhemolytic forms Are they variants of each other or may a certain strain lose and gain hemolytic ability under different conditions? In another study Orgain and Poston<sup>68</sup> report the presence of two or more species of bacteria in 6 patients with endocarditis In 3 of the patients both *Str haemolyticus* and *Str viridans* were present, in 1, *Str haemolyticus* and *Streptococcus faecalis*, and in the remainder, other bacteria

64 Rantz, L. A., Jacobs, A. H., and Kirby, W. M. M. Group A Hemolytic Streptococcus Antibodies. II. Griffith Type Agglutinin and Antistreptolysin Titers in Carriers and Non-Carriers, *J Clin Investigation* **22** 419-423 (May) 1943

65 Woods, A. C. Focal Infection, *Am J Ophth* **25** 1423-1444 (Dec) 1942

66 Rhoads, P. S., and Afremow, M. E. Streptococcal and Pneumococcal Infections of the Nose and Throat in Young Adults. Incidence, Epidemiology and Clinical Features, *Arch Int Med* **71** 443-453 (April) 1943

67 Colebrook, L., Elliott, S. D., Maxted, W. R., Morley, C. W., and Mortell, M. Infection by Nonhemolytic Group A Streptococci, *Lancet* **2** 30-31 (July 11) 1942

68 Orgain, E. S., and Poston, M. A. Mixed Infections in Bacterial Endocarditis, *Am Heart J* **23** 823-836 (June) 1942

An apparently successful attempt was made to classify strains of *Str viridans* into specific serologic types.<sup>69</sup> Of 205 strains, 66 per cent could be considered as belonging to fourteen types. Fifty per cent of the strains of *Str viridans* obtained from mouths and throats belonged to types I and II. There was no evidence that significant differences of virulence were connected with special types, invasiveness seems to depend more on the resistance of the host. It would be interesting in view of Colebrook's observation to learn if any of these strains of streptococci are clumped by the standard type-specific serums prepared with hemolytic streptococci.

In support of the contention of Bloomfield and Rantz<sup>70</sup> that scarlet fever is not a disease entity, it appears that erythrogenic toxins made by other bacteria may also cause scarlatiniform rashes. In this respect little attention seems to have been given to earlier work on the staphylococcus, but Aranow and Wood<sup>71</sup> report a case in which the causative staphylococcus produced an erythrogenic toxin which was neutralized by the usual scarlatinal antitoxin. The disease was identical with scarlet fever, yet no beta hemolytic streptococci were isolated.

*Rheumatic Fever*—In a fifteen year study of the records of 12,000 patients Cohn and Lingg<sup>72</sup> confirmed most of the previously established concepts of rheumatic fever in regard to its incidence according to age, the frequency of arthritis, myocarditis and chorea at different ages, and the eventual outcome. The peak of incidence is in the eighth year of life. At all ages polyarthritis is the most frequent single manifestation. Before the age of 10 valvular lesions are the first manifestation in 10 per cent of the patients, after 40, in 80 per cent. Ten per cent of the patients lived more than thirty years after the first attack, and 50 per cent died within nine years. The mean duration of life was thirteen years. Recurrences are most prevalent before puberty. The younger the patient at the onset of the disease, the greater is the chance that infection will be severe during the next few years. Less than one half of the children with severe infection survive childhood.

In four publications<sup>73</sup> the results of studies on chemoprophylaxis of rheumatic fever are discussed, with the idea that if predisposing infections with hemolytic streptococci can be prevented, rheumatic fever or its relapses will not occur. Small daily doses of sulfanilamide were given continually to a group of children during the winter months, and in each report the incidence of streptococcal infections and of rheumatic fever was said to be greatly reduced as compared with that in control groups not so treated. Toxic effects occurred in about 15 per cent of the subjects in one series, but were not serious. The results of these studies reemphasize the etiologic importance of group A hemolytic streptococci in rheumatic fever.

69 Solowey, M. A Serological Classification of Viridans Streptococci with Special Reference to Those Isolated from Subacute Bacterial Endocarditis, *J Exper Med* **76** 109-126 (July) 1942.

70 Aranow, H., Jr., and Wood, W. B., Jr. Staphylococcal Infection Simulating Scarlet Fever, *J A M A* **119** 1491-1495 (Aug 29) 1942.

71 Cohn, A. E., and Lingg, C. The Natural History of Rheumatic Cardiac Disease. A Statistical Study, I. Onset and Duration of Disease, *J A M A* **121** 1-8 (Jan 2) 1943, II. Manifestations of Rheumatic Activity. Recurrence, Severity of Infection and Prognosis, *ibid* **121** 113-117 (Jan 9) 1943.

72 Hansen, A. E., Platou, R. V., and Dwan, P. F. Prolonged Use of Sulfonamide Compound in the Prevention of Rheumatic Recrudescences in Children. Evaluation Based on Four Year Study on Sixty-Four Children, *Am J Dis Child* **64** 963-976 (Dec.) 1942. Thomas, C. B. Prophylactic Treatment of Rheumatic Fever by Sulfanilamide, *Bull New York Acad Med* **18** 508-526 (Aug.) 1942. Kuttner, A. G., and Reysersbach, G. The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, *J Clin Investigation* **22** 77-85 (Jan.) 1943. Chandler, C. A., and Taussig, H. B. Sulfanilamide as a Prophylactic Agent in Rheumatic Fever, *Bull Johns Hopkins Hosp* **72** 42-53 (Jan.) 1943.

Similar good results in preventing attacks of rheumatic fever were obtained when acetylsalicylic acid was used in daily doses of 4 to 6 Gm<sup>73</sup>. In only 1 of 47 patients so treated did rheumatic fever develop after a hemolytic streptococcus infection, while 57 of 139 similar but untreated patients had recurrences. If these results are confirmed, it would seem preferable to use the salicylic acid drugs in place of the sulfonamide compounds because of their relative nontoxicity.

In a clinical study<sup>74</sup> of 271 cases of rheumatic fever in children, the disease in one third of them was at first mistaken for poliomyelitis, osteomyelitis, erythematous or purpuric reactions of the skin, nephritis, sepsis, pneumonia, subacute bacterial endocarditis and other low grade infections. It was unusual that pyogenic arthritis, syphilis, scurvy, serum sickness or trichinosis which are often mentioned in differential diagnosis, were not suspected in any of the cases studied.

*Meningococcic Meningitis*—An epidemic of meningococcic meningitis as severe as the epidemic of 1929 was rampant in the winter of 1942-1943.

Branham<sup>75</sup> finds rabbit antimeningococcus serum to be superior to the horse serum. Refined, concentrated rabbit serum is sometimes ten times as potent as the horse serum now in use. Antiserum is still of value in treating meningococcic meningitis, especially in patients who cannot tolerate sulfonamide compounds. It is preferable always to determine the type of the causative meningococcus and to give specific type antiserum if possible. However, since this is not always possible, polyvalent serum may be used. In all epidemics studied in the last twenty years 90 per cent of the strains have been included in group I.

In searching for a better method by which to identify members of the *Neisseria* group of cocci Phair and co-workers<sup>76</sup> found chicken serum to be useful. Various strains of meningococci and gonococci injected into chickens evoked highly specific agglutinating serums, which provided a rapid and dependable means of identification.

#### BACILLARY DISEASES

*Bacillary Dysentery*—In the studies of Penner and Bernheim<sup>77</sup> on the genesis of dysentery, the toxins of *Bacillus dysenteriae* (Shiga) when injected into animals caused a shocklike state with compensating vasoconstriction in the small intestine and formation of a diphtheria-like membrane. The reaction is not specific, as it may be caused by other procedures. Toxin applied directly to the bowel wall caused no harmful local effect until after it had been absorbed. If the same mechanism is operative in human infection, bacillary dysentery is to be regarded not as a local disease of the intestines but as a systemic one with secondary lesions in the intestines. In this case the superiority of sulfaguanidine over the more soluble sulfonamide compounds in the treatment of bacillary dysentery may not be so great as at present supposed. Support for this view is available in Paulley's report,<sup>78</sup> in which sulfapyridine is stated to be preferable to sulfaguanidine in

<sup>73</sup> Coburn, A. F., and Moore, L. V. Salicylate Prophylaxis in Rheumatic Fever, *J. Pediat.* **21** 180-183 (Aug.) 1942.

<sup>74</sup> Hansen, A. E. Diagnosis of Rheumatic Fever, *J. A. M. A.* **121** 987-991 (March 27) 1943.

<sup>75</sup> Branham, S. A. Comparison of Rabbit and Horse Serums in Meningococcus Infection, *Pub. Health Rep.* **58** 478-483 (March 19) 1943.

<sup>76</sup> Phair, J. J., Smith, D. G., and Root, C. M. Use of Chicken Serum in the Species and Type Identification of *Neisseria*, *Proc. Soc. Exper. Biol. & Med.* **52** 72-73 (Feb.) 1943.

<sup>77</sup> Penner, A., and Bernheim, A. I. Studies on the Pathogenesis of Experimental Dysentery Intoxication, *J. Exper. Med.* **76** 271-282 (Sept.) 1942.

<sup>78</sup> Paulley, J. W. Treatment of Bacillary Dysentery in the Middle East, *Lancet* **2** 592-594 (Nov. 21) 1942.

treatment. In his experience it is of more importance to maintain a satisfactory amount of the drug in the blood than in the bowel. If the disease is mild, he gives 2 Gm of sulfapyridine, then 1 Gm every four hours until a total of 20 Gm has been given. The average period of disability in his patients was four and two-tenths days. As a commentary on the time-honored custom of giving hydragogues, his patients progressed just as favorably on the "do nothing, plus fluids" regimen. Hardy and his associates<sup>79</sup> also favor the use of the more readily absorbed sulfonamide compounds. Sulfadiazine was the most effective in rapidly controlling massive infections with the Sonne variety of bacilli, and sulfasuxidine (succinyl-sulfathiazole) was the best in ridding convalescents and passive carriers of Sonne bacilli. In mild cases of dysentery lasting several days no chemotherapeutic effects were noted with succinylsulfathiazole,<sup>79a</sup> as might be expected in disease of such short duration.

Several important detailed epidemiologic investigations were made on dysentery. One<sup>80</sup> concerned the Shiga variety in an outbreak of infection in a rural community, and the others,<sup>81</sup> the Flexner and Sonne types among inmates of an institution. The studies represent an enormous amount of bacteriologic work and bookkeeping, the difficulties of which few who have not engaged in such research can appreciate. In general they reemphasize the importance of direct contact and lack of cleanliness in the spread of the disease. In one study dysentery bacilli were found in 6.6 per cent of 13,000 stools from persons without dysentery. The prevalence of carriers varied from time to time—from none to 26 per cent. The Sonne variety of bacilli were more persistent than others. The ratio of clinical infections to carrier states in one group was as 1.7 for the Flexner variety and as 1.24 for the Sonne variety. Infection with one variety conferred no immunity against another. The probable mode of transmission in most cases is through person to person transmission of fecal pollution. There is every reason to believe that any insect crawling first on infected material and then on food may contaminate it, but only recently have ants been incriminated.<sup>82</sup>

A review of the bacteriologic aspects of dysentery bacilli has been published.<sup>83</sup>

*Typhoid Fever*—One of the few reported epidemics of typhoid fever associated with a "small colony variety" of *Eberthella typhosus*, type E, occurred in Georgia.<sup>84</sup> Apparently large colony variants appeared among the small ones on culture mediums, and their biologic reactions were similar. It is important to know that

79 Hardy, A. V., Burns, W., and DeCapito, T. Studies of the Acute Diarrheal Diseases. X. Cultural Observations in the Relative Efficiency of Sulfonamides in *Shigella Dysenteriae* Infections, *Pub Health Rep* **58** 689-693 (April 30) 1943.

79a Roberts, T. L., and Daniels, W. B. Succinylsulfathiazole in the Treatment of Bacillary Dysentery, *J. A. M. A.* **122** 651-653 (July 3) 1943.

80 Caudill, F. W., Teague, R. E., and Duncan, J. T. A Rural Shiga Dysentery Epidemic, *J. A. M. A.* **119** 1402-1406 (Aug. 22) 1942.

81 Hardy, A. V., Shapiro, R. L., Chant, H. L., and Siegel, M. Studies of the Acute Diarrheal Diseases. IX. A *Shigella Dysenteriae* Infections Among Institutional Inmates, *Pub Health Rep* **57** 1079-1094 (July 24) 1942. Watt, J., Hardy, A. V., and DeCapito, T. IX. B. *Shigella Dysenteriae* Infections Among Institutional Inmates, *ibid* **57** 1095-1102 (July 24) 1942.

82 Griffith, S. D. Ants as Probable Agents in the Spread of *Shigella* Infections, *Science* **96** 271-272 (Sept. 18) 1942.

83 Weil, A. J. Progress in the Study of Bacillary Dysentery, *J. Immunol* **46** 13-46 (Jan.) 1943.

84 Morris, J. F., Barnes, C. G., and Sellers, T. F. An Outbreak of Typhoid Fever Due to the Small Colony Variety of *Eberthella Typhosus*, *Am. J. Pub Health* **33** 246-248 (March) 1943.



unusual or variant forms of pathogenic bacteria may cause disease, and laboratory technicians must be aware of their existence so that they will not be discarded as contaminants

Edwards and Bruner<sup>85</sup> report the classification of 3,000 cultures of *Salmonella*, among which were 59 types. Practically all strains of human origin may be easily classified by using eight "O" serums in the slide agglutination test. It is gratifying that a numerical system of type nomenclature may eventually supplant the use of other, often unsatisfactory, terms

*Brucellosis*—Because some investigators reported the isolation of brucellas from the lymph nodes in Hodgkin's disease and suggested a possible relationship between the two diseases, Bloomfield<sup>86</sup> restudied the problem. He found that enlargement of superficial lymph nodes was not uncommon in brucellosis, occurring in 58 per cent of 50 cases. Therefore, because of many other similarities between the two diseases, even including the histologic changes in the lymph nodes, it is easy to confuse them. It is unlikely that brucellosis has any connection with Hodgkin's disease. Martin<sup>87</sup> reports that the mediastinal lymph nodes were shown enlarged in roentgenograms in 6 cases of undulant fever. Pressure from these nodes was thought to be the cause of a dry, irritative cough in an occasional case.

Angle and his associates<sup>88</sup> show that it is important to use standardized polyvalent antigens prepared against five to ten strains for the diagnostic serologic tests in brucellosis because of the variations of specificity encountered. Wide variations in agglutination were noted in the different tests even on the same sample of blood.

*Tetanus*—According to experience in the British Army,<sup>89</sup> tetanus bacilli are rarely found in the soil in the Middle East but are commonly present in wounds (84 per cent). In one group of 18 patients with tetanus 5 had been actively immunized with two or three doses of toxoid, but none had received antitoxin after injury. Of 7 who recovered, none had been immunized. It becomes more and more apparent that while immunization against tetanus is a valuable procedure, it is not always successful in preventing the disease or in lessening its severity. In several papers in the March issue of the *Journal of Clinical Investigation*, Mueller and his associates report the production of tetanus toxin in peptone-free media, and the production and use of toxoid made from it. This method of production is advantageous in eliminating other factors which may give rise to undesirable foreign protein reactions when tetanus toxoid is reinjected for purposes of immunization.

According to Cooke and Jones,<sup>90</sup> the immunity passively obtained with the usual prophylactic dose of 1,500 units of tetanus antitoxin lasts only about three weeks, but that obtained with large doses, e. g., 100,000 units, was demonstrable for eleven weeks. Repeated injections of tetanus toxoid did not produce antitoxic

85 Edwards, P. R., and Bruner, D. W. The Occurrence and Distribution of *Salmonella* Types in the United States, *J. Infect. Dis.* **72** 58-67 (Jan-Feb.) 1943

86 Bloomfield, A. L. Enlargement of the Superficial Lymph Nodes in *Brucella* Infection, *Am. Rev. Tuberc.* **45** 741-750 (June) 1942

87 Martin, W. S. Mediastinal Glands in Undulant Fever, *J. Michigan M. Soc.* **41** 1051-1052 (Dec.) 1942

88 Angle, F. E., Algie, W. H., and Morgan, D. Brucellosis Studies Emphasizing Strain Variation in Serologic Testing, *J. Lab. & Clin. Med.* **27** 1259-1263 (July) 1942

89 Boyd, J. S. K., and MacLennan, J. D. Tetanus in the Middle East, *Lancet* **2** 745-749 (Dec. 26) 1942

90 Cooke, J. V., and Jones, F. G. The Duration of Passive Tetanus Immunity and Its Effects on Active Immunization with Tetanus Toxoid, *J. A. M. A.* **121** 1201-1209 (April 10) 1943



immunity within several weeks. Toxoid is probably of value in immediate prophylaxis only after the subject has had previous "sensitizing" injections of toxoid.

*Tularemia*—An epizootic of tularemia among beavers in Montana is described.<sup>91</sup> Since these animals did not harbor the usual insect vectors of this disease, the source of the disease is unknown. It is possible that infected field mice living in the vicinity were the source. The beavers may have become infected by living in water polluted with urine or with carcasses of infected mice. Water in several of the streams tested contained *Pasteurella tularensis*.

Although no one has heretofore prepared an efficient vaccine against tularemia, Foshay and his co-workers<sup>92</sup> now report success. A vaccine prepared by oxidizing the bacilli with nitrous acid apparently gave complete protection to some exposed persons, and in those in whom disease did occur it was mild.

*Anthrax*—The controversy as to the best method of treating anthrax is still undecided. Gold<sup>93</sup> reviews 60 cases and concludes that sulfathiazole therapy should be given in preference to other forms of treatment. While in his experience anti-anthrax serum is helpful, the large amounts used often provoke distressing serum sickness, and neoarsphenamine is of little value. These conclusions vary from those previously published by Lucchesi, who also has had extensive experience with the disease. He uses neoarsphenamine in preference to sulfonamide compounds but agrees that antiserum is of value. Both agree that the local lesion should not be molested. It is obviously difficult to gage the comparative value of the various forms of therapy in the absence of control therapeutic tests. It is my feeling that the great majority of patients with anthrax recover without therapy and that the mortality rate is lower than is usually believed. It is almost certain that a person with a small pimple caused by anthrax without constitutional symptoms and such cases no doubt occur, will not even seek medical advice, and if he does the real nature of the infection may not be recognized without bacteriologic studies. Nevertheless because of the danger of a mild infection becoming rapidly worse and because of the fatalities which do occur, further attempts to develop efficient specific therapy are desired.

*Pertussis*—Protection against whooping cough by the injection of the toxin of *Haemophilus pertussis* is feasible but this toxin is of no value if used after the disease is established.<sup>94</sup> Dauer<sup>95</sup> who made a statistical study of pertussis points out that pertussis vaccine has not been used in a large enough number of persons or for a long enough time to permit judgment of its effect in reducing the mortality rate from the disease. Furthermore, if the mortality rate which declined spontaneously by 80 per cent in the past fifteen years, continues to decline so rapidly it will not be possible to prove statistically the value of any prophylactic measure. Since 40 per cent of deaths occur in infants under 6 months of age, vaccination if used would have to be started at an extremely early age, at an age at which the effectiveness of vaccine is not known.

91 Jellison, W. L., Kohls, G. M., Butler, W. J., and Weaver, J. A. Epizootic Tularemia in the Beaver, *Castor Canadensis*, and the Contamination of Stream Water with *Pasteurella Tularensis*, *Am J Hyg* **36** 168-182 (Sept.) 1942.

92 Foshay, L., Hesselbrock, W. H., Wittenberg, H. J., and Rodenberg, A. H. Vaccine Prophylaxis Against Tularemia in Man, *Am J Pub Health* **32** 1131-1145 (Oct.) 1942.

93 Gold, H. Anthrax. A Review of Sixty Cases with a Report on the Therapeutic Use of Sulfonamide Compounds, *Arch Int Med* **70** 785-820 (Nov.) 1942.

94 Bullova, J. G. M., and Alterman, J. Pertussis Immunity with Toxin and Antitoxin, *J A M A* **120** 886-890 (Nov. 21) 1942.

95 Dauer, C. C. Reported Whooping Cough Morbidity and Mortality in the United States, *Pub Health Rep* **58** 661-672 (April 23) 1943.

Pertussis may result in hemorrhagic, inflammatory and degenerative changes in the cerebrum, a fact which was known years ago and recently reemphasized<sup>96</sup> The disease in infancy may be the cause of eventual mental derangement, with troublesome problems of behavior and psychoses Among a group of 500 such children, nearly one half had had pertussis Diabetes insipidus has also occurred after pertussis

Two cases of septicemia with *Bacterium necrophorus* are reported and the literature on the subject reviewed by Buhler, Seely and Dixon<sup>97</sup>

*Tuberculosis*—Ordway and Medlar<sup>98</sup> reopen the controversial question of the significance of tubercle bacilli in the urine They observed that about 8 per cent of tuberculous patients had tubercle bacilli in the urine and that most of these patients had no clinical evidence of renal tuberculosis The presence of tubercle bacilli in the urine does not indicate that progressive renal tuberculosis will inevitably follow, healing may occur Surgical intervention should therefore be delayed until progressive renal destruction has been demonstrated

Other observers<sup>99</sup> state that a difference of virulence as measured by tests on guinea pigs can be detected in tubercle bacilli isolated from patients with fresh, active disease as compared with those from patients with chronic infection According to this observation, tubercle bacilli apparently gradually lose their virulence in patients as well as on artificial mediums over long periods The results need confirmation

*Leprosy*—In an epidemiologic discourse on leprosy McCoy<sup>100</sup> points out the differences in consequences after the disease had been brought to different parts of the United States For example, in Louisiana, Florida and Texas its importation led to the establishment of permanent foci, while in the midwestern states and in California the disease failed to perpetuate itself In the latter areas and elsewhere leprosy is of little importance

In regard to the treatment of leprosy McCoy<sup>101</sup> concludes that chaulmoogra oil and its derivatives are of little or no curative value and that their unpleasant side effects probably outweigh any advantage to the patient that might accrue from their use He cites similar opinions of a number of other authorities

Both fleas<sup>102</sup> and ticks<sup>103</sup> were suggested as possible vectors of leprosy

According to two Cuban dermatologists,<sup>104</sup> a change in the classification of leprosy from the cutaneous, neural and mixed types decided on at recent congresses is desirable They and many South American leprologists deem it wiser to classify

96 Levine, L. A., and Levy, S. Personality Changes and Behavior Disorders of Children Following Pertussis, *Pub Health Rep* **58** 890-894 (April 23) 1943

97 Buhler, V. B., Seely, C. W., and Dixon, D. D. *Bacterium Necrophorus* Septicemia in Man, *Am J Clin Path* **12** 380-386 (July) 1942

98 Ordway, W. H., and Medlar, E. M. Tuberculous Bacilluria. A Ten Year Study, *J A M A* **119** 937-943 (July 18) 1942

99 Corper, H. J., and Cohn, M. L. The Presence of Relatively Avirulent Tubercle Bacilli in Pulmonary Tuberculosis in Man, *J A M A* **120** 427-431 (Oct 10) 1942

100 McCoy, G. W. Observations on the Epidemiology of Leprosy, *Pub Health Rep* **57** 1935-1943 (Dec 18) 1942

101 McCoy, G. W. Chaulmoogra Oil in the Treatment of Leprosy, *Pub Health Rep* **57** 1727-1733 (Nov 13) 1942

102 Muñoz Rivas, G. Transmission of Leprosy by Fleas, *Rev Fac de med, Bogota* **10** 635-679 (April) 1942

103 Souza Araujo, H. S., cited in Transmission of Leprosy by Ticks, *Foreign Letters (Brazil)*, *J A M A* **120** 1053 (Nov 28) 1942

104 Pardo-Castello, V., and Tiant, F. R. Leprosy. The Correlation of Its Clinical, Pathologic, Immunologic and Bacteriologic Aspects *J A M A* **121** 1264-1268 (April 17) 1943

the disease on a pathologic basis as (a) lepromatous, with nodular infiltrative lesions, (b) tuberculoid, with infiltrated annular lesions, and (c) nonspecific, with macular manifestations of the skin and simple dystrophic neural disorders. Lepromatous lesions are rich in Hansen's bacilli, while in the other two forms bacilli are rare. The lepromin reaction is said to be positive only in patients with the tuberculoid type, but as it is also positive in normal people, it is unreliable as a diagnostic test. The authors' discussion of the reaction is confusing. One wonders if the new classification is actually an improvement over the old and whether it is worth while to give so much attention to clinical classification.

#### VIRAL DISEASES

*"Viral" Pneumonia*—A comprehensive review<sup>107</sup> of the subject of "viral" pneumonia and numerous clinical studies published during the year indicate how widespread the disease or group of diseases is. As reported by Duggan and Powers<sup>108</sup> and by several others,<sup>107</sup> it appeared in epidemic form in numerous military camps, and the incidence there, as elsewhere, often far exceeded that of other known types of pneumonia. In New York the board of health has now required that it be reported. Unfortunately, against the advice of all who have written on the subject, the sulfonamide compounds have been widely and unnecessarily used in its treatment. In one report<sup>108</sup> the undesirable term "sulfonamide-resistant pneumonia" is actually used to describe the disease. In another,<sup>109</sup> an equally bad term, "silent bronchopneumonia," is applied because of the typically delayed appearance of pulmonary signs of pneumonia. The authors appear to be unfamiliar with the literature on the subject. In describing an epidemic in an army camp, Campbell and his associates<sup>109a</sup> criticize the numerous names thus far suggested but add a worse one themselves, "acute bronchiolitis with associated atelectasis." In a small group of cases, according to one report,<sup>110</sup> convalescent serum gave good results in shortening the disease. The report is unconvincing as to the specificity of the effects stated.

As I stated elsewhere,<sup>111</sup> it seems that the disease entity primary atypical pneumonia, commonly called viral pneumonia, appears as a fairly uniform clinical syndrome in two general forms: (a) as a sporadic or epidemic, slightly contagious systemic disease with a relatively long incubation period; (b) as the severest type of involvement in large epidemics of mild contagious local disease of the respiratory tract with a short incubation period, usually in the cold months. If this

105 Finland, M., and Dingle, J. H. Virus Pneumonias. I. Pneumonias Associated with Known Nonbacterial Agents: Influenza, Psittacosis and Q Fever, *New England J Med* **227** 342-350 (Aug 27) 1942, II Primary Atypical Pneumonias of Unknown Etiology, *ibid* **227** 378-385 (Sept 3) 1942.

106 Duggan, L. B., and Powers, W. L. An Acute Respiratory Infection Resembling So-Called Acute Pneumonitis. A Report of Forty Cases, *J Lab & Clin Med* **28** 524-530 (Jan) 1943.

107 Dingle, J. H., Abernathy, T. J., Badger, G. F., Buddingh, G. J., Feller, A. E., Langmuir, A. D., Rueggsegger, I. M., and Wood, W. B. Primary Atypical Pneumonia, Etiology Unknown, *War Med* **3** 223-248 (March) 1943.

108 Gsell, O., and Engel, M. Sulfonamid-resistente Pneumonien, *Schweiz med Wchnschr* **72** 35-38 (Jan 10) 1942.

109 Andrus, P. M. Silent Bronchopneumonia, *Canad M A J* **47** 339-344 (Oct) 1942.

109a Campbell, T. A., Strong, P. S., Grier, G. S., and Lutz, R. G. Primary Atypical Pneumonia. A Report of Two Hundred Cases at Fort Eustis, *J A M A* **122** 723-729 (July 10) 1943.

110 Flexner, M., and Garon, M. L. Virus Pneumonia. Treatment with Convalescent Blood, *Kentucky M J* **41** 5-13 (Jan) 1943.

111 Reimann, H. A. Viral Pneumonias, *Bull New York Acad Med* **19** 177-182 (March) 1943.

classification is correct, a loose arrangement of the few known causes of the genuine viral types of pneumonia may be given as follows

<i>Sporadic Nonseasonal Forms</i>	<i>Epidemic Winter Forms</i>
Varicella	Influenza A
Vaccinia	Influenza B
Variola	Measles
Psittacosis, ornithosis, ailourosis <sup>112</sup>	Cotton rat infectious virus <sup>2 114</sup>
Lymphogranuloma venereum	Guinea pig infectious virus <sup>114</sup>
Lymphatic choriomeningitis	Unknown causes (colds, grip)
Mongoose infectious virus	
Cotton rat infectious virus <sup>114</sup>	
Feline pneumonic virus <sup>113</sup>	
Guinea pig infectious virus <sup>2 114a</sup>	
Ill defined and unknown causes	

Four newly discovered viruses have been added to the list of causes of the syndrome commonly called "virus pneumonia," as indicated in the foregoing tabulation, but the cause of the "viral pneumonia" in the majority of the cases, especially of that which occurred in epidemic form in the past winter, is as yet unknown. The four new viruses are described in the four paragraphs that follow.

A virus was obtained by Baker<sup>112</sup> from cats which, according to a preliminary report, has several characteristics that suggest its relation to the psittacosis-ornithosis-meningopneumonitis group discussed in last year's review.<sup>17</sup> If a relationship does appear, and if precedence in nomenclature is permissible, the agent may be named ailourosis virus. Antigen prepared with this virus gave complement fixation in the serum of a number of patients who had atypical pneumonia at the same time that a similar epizootic occurred among cats. The same virus was thought to be responsible in both the human patients and cats, and cross infection may have occurred.

Cats were suspected by Blake, Howard and Tatlock<sup>113</sup> as the source of another virus which may be the cause of pneumonia in man. Evidence suggests that the infection in cats was transmitted to several members of a family, sick at about the same time. Neutralization tests with patients' serum and the cat virus gave suggestive evidence that the same virus caused the disease in both species. The virus could be passed serially through kittens but not through mice, an observation which differentiates it from certain other viruses now related to atypical pneumonia.

Eaton and his associates<sup>114</sup> report the transmission and adaptation of a virus from 6 patients with atypical pneumonia to cotton rats. The virus is apparently not related to other known viruses. It was partially and irregularly neutralized by the serum of patients convalescent from pneumonia. However, rats immunized by inoculation of adapted strains were immune to reinfection with material from a human lung which produced pneumonia in controls, but rats immunized with material from the human lung were only partially resistant to rat strains. In the studies of a commission for the investigation of atypical pneumonia in an army camp,<sup>107</sup> a virus infectious for cotton rats was isolated from 4 patients. Intracytoplasmic inclusion bodies were present in the pneumonic lungs of the rats.

112 Baker, J. A. A Virus Obtained from a Pneumonia of Cats and Its Possible Relation to the Cause of Atypical Pneumonia in Man, *Science* **96** 475-476 (Nov. 20) 1942.

113 Blake, F. G., Howard, M. E., and Tatlock, H. Feline Virus Pneumonia and Its Possible Relation to Some Cases of Primary Atypical Pneumonia in Man, *Yale J. Biol. & Med.* **15** 139-165 (Dec.) 1942.

114 Eaton, M. D., Melkejohn, G., Van Herick, W., and Talbot, J. C. An Infectious Agent from Cases of Atypical Pneumonia Apparently Transmissible to Cotton Rats, *Science* **96** 518-519 (Dec. 4) 1942.

Rose and Molloy<sup>114a</sup> established a virus from 7 of 11 patients in recently weaned guinea pigs. The infection could be passed to cotton rats.

Final proof of the relation of each of these viruses to atypical human pneumonia is obviously not at hand, owing to the difficulties and uncertainties involved in the technic now available. But it is at least evident that important knowledge is accruing, and it is hoped that in time the causes of the common forms of viral pneumonia will be discovered.

In addition to the discovery of the "new" viruses, progress has been made in an attempt to clarify problems related to viruses previously reported. For example, Horsfall and his co-workers<sup>115</sup> inoculated sputum and blood from patients with atypical pneumonia into various animals but produced no infection which could be obviously propagated. In 1 case, however, primary inoculation of cotton rats caused pulmonary consolidation, but in subsequent passage the agent was lost. This experience is so much like that of Stokes and Kenny and that of Francis and Magill, who obtained similar results in the first attempts made to study the cause of viral pneumonia by using nasopharyngeal washings and blood from the patients whose cases I reported in 1938, as to suggest that we may have dealt with the same or a similar virus. At any rate, the evidence obtained in the work of Horsfall and his associates suggests that the infective agent is antigenically related to and biologically similar to the pneumonic virus of mice and to the mongoose infectious virus, both previously discovered by him. Here again, because of the difficulties of technic and the irregularities in results, conclusions must be interpreted with caution.

On somewhat more certain ground is work giving evidence of infection with ornithosis virus in human cases of "viral" pneumonia. In my own experience<sup>116</sup> in 4 of 8 cases infection with the psittacosis-ornithosis group of viruses was suggested by the indirect means of the complement fixation test. Three similar instances are reported by Favour,<sup>117</sup> and a fourth by Stickney and Heilman,<sup>118</sup> who isolated the virus. Eaton and Corey<sup>119</sup> and Smadel<sup>120</sup> found evidence of infection with this group of viruses in about 15 per cent of cases of atypical pneumonia tested. Smadel prefers not to use the term "ornithosis" but to regard the disease as due to a strain of the virus of psittacosis. Andrewes and Mills,<sup>121</sup> who isolated the virus from pigeons in England, are of similar mind. It must be recalled that complement fixation does not specifically indict any one of several viruses each of which reacts similarly, namely, those of psittacosis, ornithosis, meningopneumonitis of mice and lymphogranuloma venereum. To complicate matters more, it has recently been

114a Rose, H. M., and Molloy, E. Observations Concerning the Etiology of Primary Atypical Pneumonia, *Science* **98** 112-114 (July 30) 1943.

115 Horsfall, F. L., Curnen, E. C., Mirick, G. S., Thomas, L. and Ziegler, J. E. A Virus Recovered from Patients with Primary Atypical Pneumonia, *Science* **97** 289-290 (March 26) 1943.

116 Reimann, H. A., Havens, W. P., and Price, A. H. Etiology of Atypical ("Virus") Pneumonias with a Brief Resume of Recent Discoveries, *Arch. Int. Med.* **70** 513-522 (Oct) 1942.

117 Favour, C. B. Ornithosis (Psittacosis). A Report of Three Cases, and a Historical, Clinical and Laboratory Comparison with Human Atypical (Virus) Pneumonia, *Am. J. M. Sc.* **205** 162-187 (Feb) 1943.

118 Stickney, J. M., and Heilman, F. R. The Isolation of a Virus in Atypical Pneumonia. *Proc. Staff Meet., Mayo Clin.* **17** 369-375 (June 17) 1942.

119 Eaton, M. D., and Corey, M. Complement-Fixation in Human Pneumonitis with Group-Reactive Virus Antigens, *Proc. Soc. Exper. Biol. & Med.* **51** 165-168 (Oct) 1942.

120 Smadel, J. E. Atypical Pneumonia and Psittacosis, *J. Clin. Investigation* **22** 57-66 (Jan) 1943.

121 Andrewes, C. H., and Mills, K. C. Psittacosis (Ornithosis) Virus in English Pigeons, *Lancet* **1** 292-293 (March 6) 1943.

shown that the convalescent serums from patients recovered from atypical pneumonia also reacted with the antigens of influenza A, the pneumonic virus of mice, the cat virus reported by Baker and in low dilution with normal tissue antigen<sup>122</sup> Serum representing other infectious diseases did not give positive reactions to antigen of the pneumonic virus of mice. Ways to simplify the complexities and avoid confusion are proposed.

In another study<sup>123</sup> it was observed that blood samples from the majority of patients with primary atypical pneumonia had cold agglutinins in dilutions of from 1/10 to 1/10,000 at 0°C. It is suggested that the apparent regularity of this peculiar agglutination may be of aid in diagnosis since, according to the authors, it is rarely present in other infections. The same reaction was independently reported by Turner<sup>123a</sup> and subsequently confirmed by others<sup>123b</sup>.

*Influenza*—The subject of influenza was recently reviewed in four publications<sup>124</sup>. Additional interesting studies have also been reported. According to Shope,<sup>125</sup> lungworms, common parasites of swine, may serve as intermediate hosts for the virus of swine influenza, which the author believes to be a surviving prototype of the virus of the pandemic influenza of 1918. Apparently lungworms obtain the virus in the pig's lung. Lungworm eggs containing the virus in "masked" form are shed in the pig's feces and are in turn eaten by earthworms. The eggs hatch as larvae in earthworms, which subsequently are eaten by swine. The larvae become lungworms in pig's lungs, thus completing the cycle. The virus in swine usually lies masked and dormant in the worms or in the adjacent lung tissue, but the virus is activated and clinical influenza may develop when some additional provocative factors operate, such as cold, wet weather or some other infection, especially infection with *Haemophilus influenzae suis*.

Support for his views is given by the epidemiologic behavior of influenza in swine and the demonstration that swine lungworms and earthworms harbor the virus under natural conditions. Instead of direct transmission of the virus from pig to pig by contact, small epidemics often occur simultaneously in different localities, usually in the first four months of the year, as if provoked into activity by wet, cold weather. Field experiments suggest that, instead of the virus going like wild-fire from drove to drove and throughout a drove, it is probably widely seeded and dormant before the outbreak and is provoked into activity in the pigs almost

122 Thomas, L., Curnen, E. C., Mirick, G. S., Ziegler, J. E., and Horsfall, F. L. Complement Fixation with Dissimilar Antigens in Primary Atypical Pneumonia, *Proc. Soc. Exper. Biol. & Med.* **52** 121-125 (Feb.) 1943.

123 Peterson, O. L., Ham, T. H., and Finland, M. Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias, *Science* **97** 167 (Feb. 12) 1943.

123a Turner, J. C. Development of Cold Agglutinins in Atypical Pneumonia, *Nature, London* **151** 419 (April 10) 1943.

123b Horstmann, D. M., and Tatlock, H. Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia, *J. A. M. A.* **122** 369-371 (Jan. 5) 1943. Turner, J. C., Nisnewitz, S., Jackson, E. R., and Berney, R. Relation of Cold Agglutinins to Atypical Pneumonia, *Lancet* **1** 765-769 (June 19) 1943.

124 Horsfall, F. L. Human Influenza, in *Virus Diseases*, New York, Cornell University Press, 1943, pp. 113-143. The Present Status of the Influenza Problem, *J. A. M. A.* **120** 284-286 (Sept. 26) 1942. Francis, T. Factors Conditioning Resistance to Epidemic Influenza, in *Harvey Lectures, 1941-1942*, Lancaster, Pa., Science Press, 1942, pp. 69-99. A Rationale for Studies in the Control of Epidemic Influenza, *Science* **97** 229-235 (March 12) 1943.

125 Shope, R. E. The Swine Lungworm as a Reservoir and Intermediate Host for Swine Influenza Virus III. Factors Influencing Transmission of the Virus and the Provocation of Influenza, *J. Exper. Med.* **77** 111-126 (Feb.) 1943. The Demonstration of Masked Influenza Virus in Lungworm Larvae and Swine Under Natural Conditions, *ibid.* **77** 127-137 (Feb.) 1943. Swine Influenza, in *Virus Diseases*, New York, Cornell University Press, 1943, pp. 85-109.

simultaneously After the epidemic is over, further cases seldom occur in the following ten months In searching old literature Shope found much to support the idea that influenza in man may originate at many remote and diverse places at once It then, of course, spreads secondarily from each focus The great rapidity of spread may be more apparent than real, therefore, and represents a delusion resulting from the provocation of widely disseminated masked virus by a stimulus common to large geographic areas Descriptions of pandemics as early as 1806 by Johnson and others show that the disease appeared to spread much faster than human movement could carry it and that this could be accounted for only by assuming that multiple sources of origin existed and erupted simultaneously

In regard to the possible relationship of the virus of human influenza to that of swine influenza, Hudson, Sigel and Markham<sup>126</sup> used Hirst's technic to show that the swine virus in England is more closely related to the human type A group of viruses than is Shope's swine virus In a hypothetical discussion Andrewes<sup>127</sup> carries the matter of interepidemic latency of influenza virus further He suggests that a "basic" virus, which it seems may be represented by Shope's "masked" virus, exists devoid of specific antigen by which it could be recognized, analogous to "degraded" or "rough" forms of certain bacteria In this state the virus may live as a saprophyte in man or some other host But by passage from host to host under favorable circumstances it is enabled to increase its antigen so that it changes through several "grades" of increasing specificity and virulence until it can finally be identified as virus A, for example, with ability to invade man and cause epidemics of clinical disease Andrewes' theory obviously employs the time-honored epidemiologic concept of the gradual increase of virulence by passage through suitable hosts, a concept which in the past decade has been largely discarded as unproved in favor of the evidence that the degree of virulence of a given phase or variation of a bacterium or a virus is more stable and that variations of virulence are better explained by the appearance, spontaneous or otherwise, of variant forms, each possessing different characteristics

Francis<sup>128</sup> also regards influenza in pandemic form as a modification of a disease caused by a virus similar to those now known, and not, as some would have it, as an unrelated infection arising spontaneously in a population The forces which induced pandemicity are not known, several factors must be operative In one localized epidemic<sup>128a</sup> five slightly different antigenic strains of influenza virus were isolated Evidence is insufficient to indicate whether a number of different stable viruses exist or whether influenza virus is relatively unstable and may be constantly altered by passage through different hosts

Hirst<sup>129</sup> introduced a simple and reliable agglutinin inhibition test which depends on the fact that influenza virus causes agglutination of chicken erythrocytes and that the addition of the specific immune serum inhibits the agglutination in the presence of the homologous virus but not in that of any heterologous virus The test gives quantitative data on influenza virus and qualitative data on influenza

126 Hudson, A P , Sigel, M M , and Markham, F S Antigenic Relationship of British Swine Influenza Strains to Standard Human and Swine Influenza Viruses The Use of Chicken and Ferret Antisera in Red Cell Agglutination, *J Exper Med* **77** 467-471 (May) 1943

127 Andrewes, C H Thoughts on the Origin of Influenza Epidemics, *Proc Roy Soc Med* **36** 1-10 (Nov) 1942

128 Francis, T Epidemiology of Influenza, *J A M A* **121** 4-7 (May 1) 1943

128a Magill, T P , and Sugg, J Y Antigenically Different Strains of Virus from a Localized Influenza Outbreak, *Proc Soc Exper Biol & Med* **53** 104-106 (June) 1943

129 Hirst, G K The Quantitative Determination of Influenza Virus and Antibodies by Means of Red Cell Agglutination, *J Exper Med* **75** 49-64 (Jan) 1942



antibodies, similar to the information obtained by other more complicated tests such as virus neutralization and complement fixation. According to McClelland and Hare,<sup>130</sup> the virus is almost all adsorbed by the red cells, and the adsorbed virus retains its infectivity. It is evident therefore that both influenza and the viral pneumonias affect erythrocytes in different and peculiar manners. Hirst<sup>131</sup> also succeeded in transmitting influenza virus directly from throat washings to chick embryos in 28 of 54 trials.

The size of the pathogenic agent of influenza is said to be much smaller than 100 millimicrons as once stated.<sup>132</sup> The agent as obtained from the infected developing chick embryo by ultracentrifugation is spherical and measures only 11 millimicrons. Influenza virus is thus one of the smallest of pathogenic agents, resembling the viruses of poliomyelitis and foot and mouth disease.

*Influenza Vaccine*—Henle, Henle and Stokes<sup>133b</sup> report good results from vaccination against influenza. A group of 72 volunteers, of whom 44 had received formaldehyde-inactivated allantoic fluid vaccine made from three strains of group A virus, was exposed to active influenza A virus by inhalation. Influenza developed in only 1 of the 44 vaccinated persons and in 10 of the 28 children of the control group. Numerous mild or subclinical infections occurred among both the vaccinated and the unvaccinated subjects. The vaccine used in this experiment apparently was specific and of high potency against the strain of virus used for infection, since Bodily and Eaton<sup>134</sup> find that the immune response to single strains of type A influenza virus is often not sufficiently broad to afford protection against other viruses within the A group which may be slightly different in specific reactivity. This view might serve to explain certain failures in adequate protection with vaccine as reported by others. Furthermore, there appears to be a wide variation of specificity of immune response in human beings to any influenza vaccine. In their experience a few persons vaccinated against influenza A had antibodies also for B influenza. This may have been an anamnestic reaction after a previous infection with the B variety.

*Mild Infections of the Respiratory Tract*—The publication of Cowen, Diehl and Baker<sup>135</sup> is welcome in combating overzealous commercial advertising concerning the prevention and the treatment of colds with vitamins. In a controlled study, large doses of vitamin C alone or of vitamins A, B<sub>1</sub>, B<sub>2</sub>, C, D and nicotinic acid had no effect on the number or the severity of infections of the upper portion of the respiratory tract in adults presumably on a reasonably adequate diet. Diehl adds that even members of the control group had fewer colds than those not

130 McClelland, L., and Hare, R. The Adsorption of Influenza Virus by Red Cells and a New in Vitro Method of Measuring Antibodies for Influenza Virus, *Canad. Pub. Health J.* **32** 530-538 (Oct.) 1941.

131 Hirst, G. K. Direct Isolation of Human Influenza in Chick Embryos, *J. Immunol.* **45** 293-302 (Dec.) 1942.

132 Chambers, L. A., Henle, W., Lauffer, M. A., and Anderson, T. F. Studies in the Nature of the Virus of Influenza. II. The Size of the Infectious Unit in Influenza A, *J. Exper. Med.* **77** 265-275 (March) 1943.

133 (a) Stokes, J., Jr., and Henle, W. Studies in Methods of Prevention of Epidemic Influenza, *J. A. M. A.* **120** 16-20 (Sept. 5) 1942. (b) Henle, W., Henle, G., and Stokes, J., Jr. Demonstration of the Efficacy of Vaccination Against Influenza Type A by Experimental Infection of Human Beings, *J. Immunol.* **46** 163-175 (March) 1943.

134 Bodily, H. L., and Eaton, M. D. Specificity of the Antibody Response of Human Beings to Strains of Influenza Virus, *J. Immunol.* **45** 193-204 (Nov.) 1942.

135 Cowen, D. W., Diehl, H. S., and Baker, A. B. Vitamins for the Prevention of Colds, *J. A. M. A.* **120** 1268-1270 (Dec. 19) 1942.



included in the experiment. Placebos evidently give excellent results, and patients receiving them may give splendid testimonials for anything used to prevent colds.

On the other hand, evidence both clinical and experimental is accumulating that actual deficiency of vitamins, particularly of the vitamin B complex, has much to do with increased susceptibility to infections.<sup>136</sup> In an experimental study, monkeys given a vitamin B-free basic diet were more susceptible to infections with influenza virus and with *Str. haemolyticus*.

Stokes and Henle<sup>137a</sup> report that the vaporization of propylene glycol in a concentration of 1 to 30 or 40 million parts of air in a convalescent home for children greatly reduced the incidence of infections of the respiratory tract. Infections occurred as usual after the treatment was stopped. In another study,<sup>137</sup> ultra-violet radiation of air in nursery rooms, arranged so that "curtains" of radiation fell between infants, successfully reduced the number of infections of the respiratory tract.

Further evidence that the so-called common cold may be a syndrome of many causes is illustrated in the report of a peculiar infection by Oliphant and Dawber.<sup>138</sup> During April and May 1942, 200 cases occurred in a military barrack. The infection was presumably traced to the arrival of a person who had had bronchitis. Eleven or more days later the epidemic began. It was characterized by fever, nasal discharge, malaise, conjunctivitis, cough, sore throat, pharyngitis, bradycardia and occasionally bloody sputum. Hoarseness was the rule, but little prostration occurred. The pharynx was usually fiery red, and regional adenopathy was present. No shadows appeared in the roentgenographic lung fields, and doubtful pneumonia was present in only 2. The fever lasted one to three days, but cough and pharyngitis persisted a week in most cases. The leukocytes were seldom increased in number. The disease was not caused by the virus of influenza A or B or by any other known agent.

*Encephalitis*—Considerable progress has been made in the recognition of various forms of encephalitis and their relationship to one another. For some time after the discovery of the St. Louis type and Eastern and Western types of equine encephalitis they were regarded as distinct forms, but Hammon<sup>139</sup> classes them together as "arthropod-borne virus encephalitis." However, since the virus of the so-called Russian spring-summer encephalitis and the virus of Japanese encephalitis have also been found in arthropods in the wild state, it seems logical that Hammon should also include these infections in the aforementioned grouping. If this is done his grouping will lose significance, and it may still be desirable to apply distinctive names to the various related but slightly different neurotropic viruses. Perhaps a numerical or alphabetic nomenclature would be preferable. Geographic terms or terms signifying certain animal or insect hosts are obviously not desirable, since the St. Louis virus has been found elsewhere than near St. Louis, Western equine virus occurs in the East, and the Eastern equine virus was isolated from a patient

136 Saslaw, S., Schwab, J. L., Woolpert, O. C., and Wilson, H. E. Reaction of Monkeys to Experimental Respiratory Infections. VI. Spontaneous and Experimental Infection in Nutritional Deficiency States, *Proc. Soc. Exper. Biol. & Med.* **51**: 391-394 (Dec.) 1942.

137 Robertson, E. C., Doyle, M. E., and Tisdall, F. F. Use of Ultraviolet Radiation in Reduction of Respiratory Cross Infections in a Children's Hospital. Final Report, *J. A. M. A.* **121**: 908-914 (March 20) 1943.

138 Oliphant, J. W., and Dawber, T. R. An Epidemic of Acute Respiratory Infections of Unusual Type, *Pub. Health Rep.* **57**: 993-997 (July 3) 1942.

139 Hammon, W. M. Encephalitis: Eastern and Western Equine and St. Louis Types, as Observed in 1941 in Washington, Arizona, New Mexico and Texas, *J. A. M. A.* **121**: 560-566 (Feb. 20) 1943.

in Texas. Furthermore, many different mammals and birds may serve as sources of infection. Mosquitoes and ticks have been proved to be vectors of the viruses.<sup>140</sup>

Other interesting observations on the interrelationship and the widespread distribution of neurotropic viruses were made in Africa by Smithburn and Jacobs.<sup>141</sup> A virus called West Nile virus, of human origin, is antigenically related to the viruses of St. Louis encephalitis and Japanese B encephalitis, yet distinct from both of them. An epidemiologic survey revealed all three viruses to be active over broad expanses in Central Africa, thus more objection to the limiting geographic terms now in use is provided. One wonders if evidence of the existence of West Nile virus or an analogue will eventually be found in the United States or in Japan.

Still other apparently widely separated and supposedly unrelated neurotropic virus infections were grouped together as being similar if not identical by immunologic methods and experiments on animals. Casals and Webster<sup>142</sup> show a close relationship between the Russian tick-borne virus of spring-summer encephalitis of man and the tick-borne virus of the encephalitis of sheep called louping ill in Scotland. The broad relationship of the neurotropic strains of viruses seems to be analogous to that of the strains of rickettsias, such as the ones that cause Rocky Mountain spotted fever, São Paulo typhus and other diseases, since relatives of them or they themselves have since been found in widely scattered regions of the world. As another example, tularemia, named for Tulare County in California, has been found to be endemic in Japan and throughout Europe.

Hamsters are susceptible to infection with the viruses of Western, Eastern and West Nile encephalitis and serve as useful animals for the study of the viruses.<sup>143</sup> Electronmicrography reveals the virus of Western encephalitis to be composed of spherical or disk-shaped particles about 4 millimicrons in diameter.<sup>144</sup>

The viruses of lymphogranuloma venereum,<sup>145</sup> rubella<sup>146</sup> and herpes simplex<sup>147</sup> were isolated from the spinal fluid of patients with meningoencephalitis. In the case of lymphogranuloma venereum, symptoms of encephalitis were dominant, and the inguinal lymph nodes were only slightly enlarged. Under these circumstances the diagnosis cannot be made clinically but rests on (1) the inoculation of spinal fluid into mice, (2) the complement fixation test made with the patient's serum and the specific antigen, (3) the Frei test and (4) biopsy of a lymph node. In the other

140 Hammon, W. M., and Reeves, W. C. *Culex tarsalis* Coq., a Proven Vector of St. Louis Encephalitis, *Proc Soc Exper Biol & Med* **51** 142-143 (Oct.) 1942. Hammon, W. M., Reeves, W. C., and Gray, M. Mosquito Vectors and Inapparent Animal Reservoirs of St. Louis and Western Equine Encephalitis Viruses, *Am J Pub Health* **33** 201-207 (March) 1943.

141 Smithburn, K. C., and Jacobs, H. R. Neutralization Tests Against Neurotropic Virus with Sera Collected in Central Africa, *J Immunol* **43** 9-23 (May) 1942. Smithburn, K. C. Differentiation of West Nile Virus from the Viruses of St. Louis and Japanese B Encephalitis, *ibid* **43** 25-31 (May) 1942.

142 Casals, J., and Webster, L. T. Close Relation Between Russian Spring-Summer Encephalitis and Louping-Ill Viruses, *Science* **97** 246-248 (March 12) 1943.

143 Watson, D. W., and Smadel, J. E. Susceptibility of Hamsters to Peripheral Inoculation of Western, Eastern, and West Nile Encephalitis Viruses, *Proc Soc Exper Biol & Med* **52** 101-104 (Feb.) 1943.

144 Sharp, G. G., Taylor, A. R., Beard, D., and Beard, J. V. Electron Micrography of the Western Strain Equine Encephalomyelitis Virus, *Proc Soc Exper Biol & Med* **51** 206-207 (Nov.) 1942.

145 Sabin, A. B., and Aring, C. D. Meningoencephalitis in Man Caused by the Virus of Lymphogranuloma Venereum, *J A M A* **120** 1376-1381 (Dec. 26) 1942.

146 Bradford, R. I. C. Two Cases of Rubella Meningoencephalitis, *Lancet* **1** 312-313 (March 13) 1943.

147 Armstrong, C. Herpes Simplex Virus Recovered from the Spinal Fluid of a Suspected Case of Lymphocytic Choriomeningitis, *Pub Health Rep* **58** 16-21 (Jan. 1) 1943.

case, lymphocytic choriomeningitis was suspected, but the virus of herpes simplex was isolated. Reference is made on page 424 to the occurrence of lymphocytic meningoencephalitis in patients with pleurodynia. These examples show that numerous unsuspected known viruses may give rise to forms of encephalitis and besides, there is evidence from the reports of Price<sup>148</sup> and of Woodland and Smith<sup>149</sup> that outbreaks of encephalitis occur from time to time in which none of the known agents seems to be implicated.

It is hard to decide whether or not reference should be made to the numerous original articles and discussions of other papers on the subject of encephalitis published by E. C. Rosenow during the past year. Practically all deal with the ideas that he has held for years, namely, the relationship of streptococci and their supposed filtrable state to encephalitis and the use of antiserum against these streptococci. New departures in his views are the demonstrations of "streptococcus antigen" and of the streptococci in question from the mud of a lake bottom, from air at a high altitude and from rain and snow in an epidemic area. The "encephalitic type" of streptococci was also isolated from dying fish, and he apparently finds it necessary to inform his readers that the "transmission of encephalitis by bites of mosquitoes in this species was out of the question."<sup>150</sup> Most investigators over the years have found it difficult if not impossible to accept the majority of Rosenow's tenets, but because of the feeling that, after all, "there may be something to it," they have been reluctant to discard them in their entirety as fantastic obfuscation.

*Poliomyelitis*—In a discussion of the genesis of poliomyelitis Sabin<sup>151</sup> suggests that the so-called signs of meningeal irritation should be regarded as the early signs of injury of the neurons instead. Some neurons may be completely destroyed, others, partly so, in which partial or complete recovery may occur. The portion of the central nervous system which is involved depends on the neural connections along which the virus spreads from the peripheral source. There is reason to believe that the virus invades from the alimentary tract through the fifth, seventh, ninth and tenth cranial nerves to cause the bulbar form of poliomyelitis. To affect the lower extremities, the virus may traverse the afferent fibers from the intestines by way of the dorsal root ganglions. In the bulbar form of poliomyelitis there is a heavy concentration of neuronal lesions in the medulla, with fewer in the cord, in the spinal type the reverse occurs.

The incubation period of poliomyelitis as far as Casey<sup>152</sup> could measure was from five to thirty-five days, with an average of twelve days.

A crystalline protein fraction which may represent the virus of poliomyelitis, or at least a protein on which it is adsorbed, was obtained by Racker from the brains of infected mice.<sup>153</sup> In other experiments Boudillon and Moore<sup>154</sup> obtained an apparently "pure" virus by ultracentrifugation.

148 Price, A. H. Sporadic Meningoencephalitis of Undetermined Etiology, abstracted, *J. Clin. Investigation* **21** 629 (Sept.) 1942.

149 Woodland, J. C., and Smith, E. M. Acute Encephalitis. Mild Epidemic Observed at Station Hospital, Fort Sam Houston, Texas, *J. A. M. A.* **120** 358-361 (Oct. 3) 1942.

150 Rosenow, E. C. The Relation of Neurotropic Streptococci to Encephalitis and Encephalitic Virus, *Proc. Staff Meet., Mayo Clin.* **17** 551-560 (Nov. 4) 1942.

151 Sabin, A. B. Pathology and Pathogenesis of Human Poliomyelitis, *J. A. M. A.* **120** 506-511 (Oct. 17) 1942.

152 Casey, A. E. The Incubation Period in Epidemic Poliomyelitis, *J. A. M. A.* **120** 805-807 (Nov. 14) 1942.

153 Racker, E. Crystallization of a Protein from Poliomyelitis Infected Mouse Brain, *Science* **96** 364-365 (Oct. 16) 1942.

154 Boudillon, J., and Moore, D. H. Attempts at Purification of a Murine Strain of Human Poliomyelitis Virus, *Science* **96** 541-542 (Dec. 11) 1942.

Dauer has some discouraging things to say about recent studies on poliomyelitis. In spite of all the research in the past twenty years, little new information has accrued, the manner of person to person transmission is unknown, there is insufficient evidence to incriminate water as a medium of conveyance of practical importance, and there is no proof that insects may serve as vectors or reservoirs or that reservoirs of infection exist in lower animals.<sup>154a</sup>

Apropos of Rosenow's numerous publications on the subject of poliomyelitis, the same remarks as were made under the heading "Encephalitis" apply. In a recent paper<sup>155</sup> he reports the use of a cutaneous test for the diagnosis of poliomyelitis and as a guide for the amount of "poliomyelitis antistreptococcic" serum to be used in treatment. His view that a specific streptococcus is the cause of poliomyelitis is at variance with practically all other evidence.

*Epidemic Keratoconjunctivitis*—During the summer of 1941 there was an outbreak of epidemic keratoconjunctivitis in Hawaii chiefly among artisans and others engaged in war work. By early autumn the infection had been carried to California, where a similar occupational group was involved. The peak of the epidemic occurred in January 1942. Since then the infection has appeared in the eastern part of the United States, where it also reached epidemic proportions. As usually happens when unfamiliar epidemics occur, it was at first believed to be a "new" disease, but records suggest that similar ones had been reported since 1890 in Europe and the Orient. It is of especial importance at present because it causes disability lasting from one to five weeks among workers and others essential to the war effort.

In a study of 80 cases in New York, Sanders and his group<sup>156</sup> succeeded in isolating a filterable virus in 2 of 9 cases. The virus was apparently identical with one previously obtained in similar cases and was neutralized by the serum of a patient who had recovered from the infection. Furthermore, the demonstration of neutralizing antibodies in the blood of other similar patients adds support to the causative relation of the virus to the disease. These observations await further confirmation.

The infection is apparently spread by contact with infected material and is favored by irritation of the conjunctiva by abrasive dust, intense light or other irritants. The incubation period lasts from five to twelve days. One eye is usually affected. The local symptoms are those of intense inflammation, but in from 25 to 50 per cent of patients, more or less severe systemic symptoms occur. Preauricular adenitis is common. Vision is often impaired by corneal changes which for the most part eventually heal without defect. Sulfonamide compounds are said by some to be "almost" specific,<sup>157</sup> and in a few cases the use of "convalescent" serum from patients recovered from the infection seemed to cause clinical improvement, but it is probable that in this as in other forms of conjunctivitis spontaneous

154a Dauer, C. C. Poliomyelitis in the United States in 1942 and a Summary of Its Prevalence from 1933 to 1942 Inclusive, *Pub. Health Rep.* **58** 937-949 (June 18) 1943.

155 Rosenow, E. C. A Diagnostic Cutaneous Reaction in Acute Poliomyelitis, *Proc. Staff Meet., Mayo Clin.* **18** 118-128 (April 21) 1943.

156 Sanders, M., and Alexander, R. C. Epidemic Keratoconjunctivitis. I. Isolation and Identification of a Filterable Virus, *J. Exper. Med.* **77** 71-93 (Jan.) 1943. Sanders, M., Gulliver, F. D., Forchheimer, L. L., and Alexander, R. C. Epidemic Keratoconjunctivitis. Clinical and Experimental Study of an Outbreak in New York City, Further Observations on the Specific Relationship Between a Virus and the Disease, *J. A. M. A.* **121** 250-255 (Jan.) 1943.

157 Braley, A. E., and Sanders, M. Treatment of Epidemic Keratoconjunctivitis. Preliminary Report of Ten Cases, *J. A. M. A.* **121** 999-1000 (March 27) 1943.

recovery without therapy is the rule. According to circular letter no. 14 of the Surgeon General of the Army "there is no specific therapy."

To prevent the disease from spreading, patients should be strictly isolated, and physicians in contact with the disease should use great care to avoid carrying the infection to others.

*Yellow Fever*—Although jaundice no longer seems to occur after vaccination against yellow fever, the cause of that which formerly appeared has never been determined with certainty.<sup>158</sup> It is the consensus that the human serum that was a part of the vaccine then used carried a contaminating infectious agent. However, because of otherwise unexplained variations in the incidence of jaundice in equivalently vaccinated persons, the possibility of some extrinsic environmental factor also entered the discussion. The jaundice resembled "catarrhal jaundice" clinically but differed in its long incubation period and its predilection for adults. The vaccine as prepared now is composed only of an aqueous extract of chick embryos infected with "attenuated" 17 D strain of yellow fever virus.<sup>159</sup> It contains considerably more antigen than the older serum-containing vaccine.

Interesting in respect to the probability that the serum caused the jaundice is the study of Beeson,<sup>160</sup> who collected older literature concerning the development of jaundice in patients treated for various reasons by injection of human plasma serum or lymph and added 7 cases of his own. The resulting jaundice resembled the so-called catarrhal form but had an "incubation period" of from one to seven months, like that which followed vaccination against yellow fever.

Fox and his co-workers<sup>161</sup> in Brazil report 199 cases of encephalitis after vaccinating 55,000 persons against yellow fever. To explain this untoward effect the authors, not wishing to ascribe its cause to some adventitious factor, suggest that a variation occurred in the virus composing a certain lot of vaccine which rendered the vaccine neurotropic. It has always seemed to me that a similar explanation suited the problem of jaundice, but no evidence for it is forthcoming.

Fox and Cabral<sup>162</sup> demonstrated that in the great majority of vaccinated adults the protective action persisted for four years. The duration of relatively strong immunity was much shorter in young persons and disappeared in 10 per cent of them after three years. Children apparently do not react antigenically as well as adults and seem to require vaccination at shorter intervals.

*Other Viral Diseases*—The relationship between herpes zoster and varicella is still uncertain. Many believe the two diseases to be caused by unrelated agents while others believe them to be closely related, assuming that the same virus has variant forms, one causing one and the second the other disease. Garland<sup>163</sup> adds evidence in support of the latter view by reporting 3 cases in which varicella

158 Fox, J. P., Manso, C., Penna, H. A., and Madureira, Para. Observations on the Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, *Am J Hyg* **36** 68-116 (July) 1942.

159 Hargett, M. V., Burruss, H. W., and Donovan, A. Aqueous-Base Yellow Fever Vaccine, *Pub Health Rep* **58** 505-512 (March 26) 1943.

160 Beeson, P. B. Jaundice Occurring One or Two Months After Transfusion of Blood or Plasma. Report of Seven Cases, *J A M A* **121** 1332-1334 (April 24) 1943.

161 Fox, J. P., Lennette, E. H., Manso, C., and Souza Aguiar, J. R. Encephalitis in Man Following Vaccination with 17 D Yellow Fever Virus, *Am J Hyg* **36** 117-142 (Sept) 1942.

162 Fox, J. P., and Cabral, A. S. Duration of Immunity Following Vaccination with the 17 D Strain of Yellow Fever Virus, *Am J Hyg* **37** 93-102 (Jan) 1943.

163 Garland, J. Varicella Following Exposure to Herpes Zoster, *New England J Med* **228** 336-337 (March 18) 1943.

developed fourteen days after exposure to a patient with typical herpes zoster. Many others have previously reported the reverse—namely, herpes zoster occurring during and after outbreaks of varicella.

In an outbreak of smallpox in Glasgow, Scotland, an obscure febrile condition developed in 40 of 92 persons who had been in close contact with the disease.<sup>164</sup> All of them were vaccinated after contact, and the febrile reaction occurred from six to thirteen days afterward. In 30 vaccine was the cause, in 2 the cause was smallpox, in the remaining 8 it was probably smallpox, but the latter was so atypical and mild that it would ordinarily not be diagnosed as such. Evidence is therefore presumptive that in an epidemic a proportion of the patients will have a mild type of smallpox or that in these patients vaccination has modified the severity of the attack.

Smallpox was at its lowest ebb in the United States in 1941, with only 1,432 cases reported. A small outbreak occurred in central Pennsylvania in 1942.

In Gallagher's<sup>165</sup> experience in a boys' school specific immune globulin as used to prevent measles was far from reliable. In 14 boys the presumed adequate dosage failed even to modify the severity of the disease. The degree of protection in the treated group as compared with an untreated control group failed to give evidence of its efficiency in the age group 13 to 18.

During the last five years a filtrable virus has been shown to be the cause of rubella, or German measles. An increase in the number of neurologic symptoms in the form of neuritis and encephalitis has also been noted. Habel<sup>166</sup> injected nasal washings obtained from patients early in the disease into 41 monkeys and observed that a rash appeared in 12 animals. The rash with leukopenia, relative lymphocytosis and slight fever were the only evidences of infection. Reinoculation of monkeys several weeks later showed that specific immunity had developed in only 2 of 7 animals. No cross immunity to rubeola was evident.

The virus of rabies was isolated from the brain of a patient in whom the infection was not suspected during life.<sup>167</sup> The antemortem diagnosis was psychoneurosis and acute anxiety. After the diagnosis was corrected, further inquiry revealed a history of the patient having been bitten by a dog.

Andrewes and his associates<sup>167a</sup> tested the therapeutic effects of 115 agents, including penicillin, on several viral infections. None had any beneficial effect except the sulfonamide compounds, which influenced lymphogranuloma venereum.

#### RICKETTSIAL DISEASES

Typhus fever was contracted by 12 workers in a laboratory probably by inhaling infective droplets during intranasal inoculation of mice with the murine strain of typhus rickettsias.<sup>168</sup> It was disappointing to learn that each of these workers

164 Napier, W., and Insh, A. M. Febrile Reactions Among Smallpox Contacts, *Lancet* **2** 483-484 (Oct. 24) 1942.

165 Gallagher, J. R. Inefficiency of Immune Globulin in the Prophylaxis of Measles During Adolescence, *Am. J. M. Sc.* **203** 880-882 (June) 1942.

166 Habel, K. Transmission of Rubella to Macacus Mulatta Monkeys, *Pub. Health Rep.* **57** 1126-1139 (July 31) 1942.

167 Schaeffer, M., and Leider, A. G. Recovery of Rabies Virus from the Brain of an Undiagnosed Case, *J. Lab. & Clin. Med.* **27** 1263-1267 (July) 1942.

167a Andrewes, C. H., King, H., and van den Ende, M. Chemotherapeutic Experiments with the Viruses of Influenza A, Lymphogranuloma Venereum and Vaccinia. *J. Path. & Bact.* **55** 173-181 (April) 1943.

168 van den Ende, M., Stuart-Harris, C. H., Harries, E. H. R., and Steigman, A. J. Laboratory Infections with Murine Typhus, *Lancet* **1** 328-332 (March 13) 1943.

had been vaccinated either with the Castaneda vaccine, composed of killed murine typhus rickettsias, or the Cox type of vaccine, composed of killed epidemic typhus rickettsias, a short time prior to infection. On the other hand, it is possible that the vaccine lessened the severity of the disease, since only 3 patients had moderately severe and the rest mild typhus and may not have been recognized as having typhus had the disease not been in mind.

A similar experience was reported<sup>169</sup> from an American laboratory where two workers previously immunized with three and four doses, respectively, of Cox yolk sac vaccine contracted a mild form of epidemic typhus, one while harvesting egg cultures, the other by accidentally splashing virus into her eye. In both cases the disease was mild and could easily have been mistaken for influenza had not the history been so clear.

Castaneda<sup>170</sup> ascribes the failure of vaccine to give adequate protection in his experience to lack of specificity of vaccine made with murine strains against infection with the epidemic strain. By adding antigen of the epidemic strain to the murine vaccine, a more potent vaccine was devised.

Nearly 3,700 cases of typhus were reported in the United States in 1942, numbers of them from California, where the infection was thought not to occur, however, 229 cases have appeared there since 1916.<sup>171</sup> It is believed that probably not more than 20 per cent of cases are reported, so that the disease is no doubt far more prevalent than the statistics lead one to believe.<sup>172</sup>

During experimental studies to determine the incidence of natural typhus infection among wild rats in Savannah, Ga.,<sup>173</sup> guinea pigs inoculated with rat tissues often died. In searching for the cause of death, obviously not caused by typhus, toxoplasma was found. Nearly 9 per cent of the rats studied were infected with this protozoan agent.

*Other Rickettsial Infections*—South American workers, who unfortunately call a form of spotted fever "Brazilian typhus," show that dogs may be artificially infected with the agent and that natural infection occurs as well.<sup>174</sup> Dogs and the ticks which infest them may therefore serve as important sources of infection. Many outbreaks occur in households in which dogs, dog ticks and bedbugs are found to be infected. Since dogs are also incriminated in *fièvre boutonneuse*, or Mediterranean spotted fever, it is suggested that they may be natural carriers of the disease in the United States. A tick, *Amblyomma americanum*, known to be a vector of spotted fever in South America, is now for the first time believed to be a natural vector in this country.<sup>175</sup> In a small outbreak of spotted fever in Texas, ticks of this species alone were present.<sup>176</sup> Infected nymphs of *Amblyomma*

169 Gold, H., and Fitzpatrick, F. Typhus Fever in a Previously Vaccinated Laboratory Worker, *J. A. M. A.* **119** 1415-1416 (Aug. 22) 1942.

170 Castaneda, M. R. Bivalent Typhus Vaccine of High Immunizing Value, *Science* **96** 304 (Sept. 25) 1942.

171 Halverson, W. L. Typhus Fever in California, *California & West Med.* **51** 196-200 (Sept.) 1942.

172 Eskey, C. R. Murine Typhus Fever Control, *Pub. Health Rep.* **58** 631-638 (April 16) 1943.

173 Perrin, T. L., Brigham, G. D., and Pickens, E. G. Toxoplasmosis in Wild Rats, *J. Infect. Dis.* **72** 91-96 (Jan.-Feb.) 1943.

174 Dogs as Healthy Carriers of Brazilian Typhus, *Foreign Letters, J. A. M. A.* **121** 65-66 (Jan. 2) 1943.

175 Parker, R. R., Kohls, G. M., and Steinhaus, E. A. Rocky Mountain Spotted Fever Spontaneous Infection in the Tick *Amblyomma Americanum*, *Pub. Health Rep.* **58** 721-729 (May 7) 1943.

176 Anigstein, L., and Bader, M. N. New Epidemiological Aspect of Spotted Fever in the Gulf Coast of Texas, *Science* **96** 357-358 (Oct. 16) 1942.



were also found in Oklahoma. In previous experience in South America a tick of a species of *Amblyomma* harboring spotted fever was taken from a pet dog.

A brief clinical discussion of trench fever has been published.<sup>177</sup> A case of Q fever was reported from South Carolina,<sup>178</sup> the diagnosis of which is even more doubtful than that of the case described in Montana in 1941. The only evidence of Q fever was a specific complement fixation test positive in the low dilution 1:4. Experimental studies on Q fever<sup>179</sup> showed that the causative rickettsias persisted for a month or more in various tissues after the animals had recovered from the disease.

Philip<sup>180</sup> calls attention to the confusion which has arisen in the nomenclature of pathogenic rickettsias and properly recommends the adherence to accepted taxonomic procedure. According to Steinhaus and Paiké,<sup>180a</sup> several sulfonamide compounds, atabrine and tyrothricin (an extract of *Bacillus brevis* of Dubos) had little or no therapeutic effect in experimental Rocky Mountain spotted fever.

#### FUNGUS DISEASES

*Coccidioidomycosis*—Because of certain similarities of pulmonary tuberculosis and coccidioidomycosis, with regard both to the acute stage and to the end results in the lungs, with roentgenographic evidence of cysts and areas of calcification, error in diagnosis has no doubt often occurred.<sup>181</sup> In studying large groups of Indians who reacted negatively to the tuberculin test despite roentgenograms of the lungs which showed shadows suggestive of healed tuberculosis, Aronson and his associates<sup>182</sup> suspected that coccidioidomycosis may have been the cause of this phenomenon. In different groups tested with coccidioidin, injected intradermally, the incidence of positive reactions varied greatly from place to place—from none to 94 per cent. It is very likely that in many of these persons who failed to react to tuberculin, infection with the fungus *Coccidioides immitis* may have been the cause of the calcified pulmonary nodules.

In studies to determine how widespread infection with this fungus is and whether it is being "spread" by human or other carriers, Schenken and Palik<sup>183</sup> concluded that the great majority of cases were in, or originated in, California, Texas, Arizona and New Mexico. In only 5 cases was the source of infection apparently outside this area. Cases described in Minnesota and Virginia were rejected because of lack of proof of the diagnosis. It is fairly certain that the infection is not spreading and that local factors which favor the existence of the fungus control the incidence of infection in persons and in animals residing in these areas.

177 Hurst, A. Trench Fever, *Brit. M. J.* **2** 318-320 (Sept. 12) 1942.

178 Zemp, F. E. Q Fever, *J. A. M. A.* **121** 828-829 (March 13) 1943.

179 Parker, R. R., and Steinhaus, E. A. American and Australian Q Fevers. Persistence of Infectious Agents in Guinea Pig Tissues After Defervescence, *Pub. Health Rep.* **58** 523-527 (March 26) 1943.

180 Philip, C. B. Nomenclature of the Pathogenic Rickettsiae, *Am. J. Hyg.* **37** 301-309 (May) 1943.

180a Steinhaus, E. A., and Parker, R. R. Experimental Rocky Mountain Spotted Fever. Results of Treatment with Certain Drugs, *Pub. Health Rep.* **58** 351-352 (Feb. 26) 1943.

181 Winn, W. A., and Johnson, G. H. Primary Coccidioidomycosis. A Roentgenographic Study of Forty Cases, *Ann. Int. Med.* **17** 407-422 (Sept.) 1942.

182 Aronson, J. D., Saylor, R. M., and Parr, E. I. Relationship of Coccidioidomycosis to Calcified Pulmonary Nodules, *Arch. Path.* **34** 31-72 (July) 1942.

183 Schenken, J. R., and Palik, E. E. Coccidioidomycosis in States Other than California with Report of a Case in Louisiana, *Arch. Path.* **34** 484-494 (Sept.) 1942.



On the other hand, Aronson and Gallagher<sup>184</sup> in testing boys in a school in Massachusetts found 17 of 680 students reacting positively to coccidioidin. Of these, 8 had never been west of the Mississippi River. Five of the 17 failed to react to tuberculin and had calcified areas in their lungs. Whether the positive reactors actually had had coccidioidomycosis, and, if so, where they were infected, is unknown.

In another case of chronic pneumonitis, supposedly tuberculosis, Baldwin<sup>185</sup> isolated an acid-fast chromogenic bacillus which was not virulent for guinea pigs, rabbits or mice. It is obvious that certain patients who have tuberculosis-like chronic pulmonary diseases may be infected with agents other than the tubercle bacillus, and careful bacteriologic investigations should be made in all doubtful cases. It is also evident that pathologists cannot always make a final diagnosis of tuberculosis by the demonstration of tubercles alone. There are many causes of tubercle formation besides *Mycobacterium tuberculosis*.

Emmons and Ashburn<sup>186</sup> present further epidemiologic data on coccidioidomycosis. A high percentage of rodents in endemic areas are infected with the fungus. Because of this, they are regarded as a reservoir of infection important in the dissemination of the infection to man. However, it seems to me that rodents, like man, which live in an endemic area are merely incidentally infected because of intimate exposure to a fungus which grows in local vegetation of soil and do not necessarily play a role in spreading the disease to other places where the fungus cannot grow. In regions where man has acquired infection, cattle, dogs and sheep may also harbor the fungus<sup>187</sup>.

Emmons and Ashburn isolated a hitherto undescribed fungus from rodents which they call *Haplosporangium parvum* n. sp. This fungus causes granulomatous lesions and may also cause disease in human beings. Cutaneous tests made with extracts of this fungus gave positive reactions in many persons who also reacted positively to coccidioidin. The two fungi may be related. Furthermore, cultural characteristics of *H. parvum* are similar to those of *Blastomyces dermatitidis* and *Histoplasma capsulatum*, both of which are pathogenic for man.

*Trichophytosis or "Athlete's Foot"*—Much nonsense has been published on this subject, and thousands of dollars have been wasted as a result of commercial advertising and subsequent use of a variety of remedies for its treatment. According to a recent view,<sup>188</sup> the condition is seldom contagious and is chiefly caused by improper care of the feet. It is brought about by chafing and maceration of the skin resulting from continued moisture, particularly during warm weather which favor the growth and invasion of the fungus habitually present. Cleanliness and properly fitting ventilated shoes are of far more importance in preventing the condition than are the numerous remedies for its treatment.

184 Aronson, J. D., and Gallagher, J. R. Sensitivity to Coccidioidin Among Boys in an Eastern Preparatory School, *Am J Pub Health* **32** 636-639 (June) 1942.

185 Baldwin, E. R. Non-Pathogenic Acid-Fast Bacilli. I. A Case of Chronic Pneumonitis Associated with a Non-Pathogenic Acid-Fast Bacillus, *Am Rev Tuberc* **45** 756-761 (June) 1942.

186 Emmons, C. W., and Ashburn, L. L. The Isolation of *Haplosporangium parvum* N. Sp. and *Coccidioides immitis* from Wild Rodents. Their Relationship to Coccidioidomycosis, *Pub Health Rep* **57** 1715-1727 (Nov 13) 1942.

187 Stiles, G. W., and Davis, C. L. Coccidioidal Granuloma (Coccidioidomycosis). Its Incidence in Man and Animals and Its Diagnosis in Animals, *J A M A* **119** 765-769 (July) 1942.

188 Sulzberger, M. B., Baer, R. L., and Hecht, R. Common Fungous Infections of the Feet and Groins. Negligible Role of Exposure in Causing Attacks, *Arch Dermat & Syph* **45** 670-675 (April) 1942.

Dogs, in addition to being sources of infection for the fungous diseases histoplasmosis and coccidioidomycosis, are also possible sources for *Blastomyces dermatitidis*, according to Foshay and Madden<sup>189</sup>

A ringworm-like infection of the skin in children who had played together and with kittens has been reported<sup>190</sup> Examination of one of the kittens showed it to be infected with the fungus *Microsporon lanosum*

A rare case of infection resembling subacute bacterial endocarditis was caused by *Histoplasma capsulatum*<sup>190a</sup>

#### MISCELLANEOUS INFECTIONS

*Leptospirosis*—Since the value of convalescent serum in the treatment of Weil's disease is so uncertain, Larson<sup>191</sup> tested the effects of serotherapy in infected mice Serum from convalescent patients and immune serum prepared by inoculating rabbits with *Leptospira icterohaemorrhagiae* were used The protective antibodies were in the globulin fraction and could be concentrated by suitable means Both forms of serum prevent death in young mice if given on or before the fourth day after infection

*Trichinosis*—In a discussion of the modern aspects of trichinosis, Wright<sup>192</sup> points out how misleading much of the earlier information is, particularly in regard to symptoms Trichinosis varies greatly in its clinical manifestations, depending on the number of larvae ingested, on reinfections and on the general condition of the host The so-called typical clinical picture described in textbooks is more the exception than the rule Large surveys indicate that about 16 per cent of people in this country are infected with *Trichinella* It is believed that the incidence can be reduced by feeding hogs cooked rather than raw garbage

In 2 cases of trichinosis of my own,<sup>193</sup> studied over many months, the typical microscopic lesions and the clinical picture of periarteritis nodosa developed These later disappeared, and chronic nephritis developed, which in 1 case was fatal The appearance of the lesions of periarteritis nodosa suggested that they were incited by trichinosis and were allergic in nature, in turn suggesting that trichinosis may be one of the causes of periarteritis nodosa

A serologically active polysaccharide, which may be helpful in diagnostic tests, was obtained from *Trichinella*<sup>194</sup>

*Schistosomiasis*—In an article giving the latest information on schistosomiasis of the Manson or intestinal type, Koppisch<sup>195</sup> points out how important it will be for physicians in this country and elsewhere who have had no experience with it to be able to recognize the disease Beyond doubt a certain percentage of the military

189 Foshay, L., and Madden, A. G. The Dog as a Natural Host for *Blastomyces Dermatitidis*, *Am J Trop Med* **22** 565-569 (Sept.) 1942

190 Botvinnick, I., Peck, S. M., and Schwartz, L. An Outbreak of *Microsporon Lanosum* Infection from a Kitten, *Pub Health Rep* **58** 317-319 (Feb. 19) 1943

190a Broders, A. C., Dochat, G. R., Herrell, W. E., and Vaughn, L. D. Histoplasmosis Producing Vegetative Endocarditis. Review of Literature with Report of a Case, *J A M A* **122** 489-492 (June 19) 1943

191 Larson, C. L. Treatment of Young White Mice Infected with *Leptospira Icterohaemorrhagiae* with Immune Serum, *Pub Health Rep* **58** 10-15 (Jan. 1) 1943

192 Wright, W. A. A Consideration of the Clinical and Public Health Aspects of Trichinosis, *Journal-Lancet* **62** 389-393 (Nov.) 1942

193 Reimann, H. A., Price, A. H., and Herbut, P. A. Trichinosis and Periarteritis Nodosa. Differential Diagnosis, Possible Relationship, *J A M A* **122** 274-279 (May 29) 1943

194 Melcher, L. R., and Campbell, D. H. A Serologically Active Polysaccharide from *Trichinella Spiralis*, *Science* **96** 431-432 (Nov. 6) 1942

195 Koppisch, E. Manson's Schistosomiasis, *I A M A* **121** 936-942 (March 20) 1943

personnel who serve in regions where the disease is endemic will contract it and return home infected. The disease must be diagnosed promptly and specifically treated before it causes irreparable cirrhosis of the liver or other injury, and before the ova escape to establish endemic foci in this country. Although, according to the author, none of the planorbids or mollusks which are capable of acting as intermediate hosts for these schistosomes occur in the United States, it must be remembered that in 1941 Penner<sup>196</sup> found in a Minnesota pond a strain of *Schistosomium douthitti* with which he was able to infect monkeys. Only further study will show whether the certain mollusks which occur in this country may harbor other pathogenic schistosomes.

Two cases of imported schistosomiasis (*Schistosoma haematobium*) were reported from Michigan<sup>197</sup>. The authors refer to several other cases in the United States.

In a preliminary report Anderson describes the cultivation of micro-organisms resembling Donovan bodies from patients with venereal lymphogranuloma.<sup>197a</sup>

*Malaria*—Coggeshall<sup>198</sup> calls attention to the danger of malaria becoming widespread in the United States after the return of troops who have been infected elsewhere. Throughout the country important anopheline mosquito vectors are potential transmitters of infection from patients with imported malaria or from healthy carriers, to say nothing of the possibility of the introduction of other dangerous varieties of mosquitoes. The latter accident occurred in Brazil when *Anopheles gambiae* was accidentally introduced and eventually caused more than 14,000 deaths from malaria before it was eradicated. The author warns that methods designed to control malaria by curbing the larval or adult development of the mosquito, by attempts to prevent mosquito bites in man and by attempts to prevent or cure the disease with drugs have all failed in their purpose. It is disappointing to learn that atabrine (now officially recognized as quinacrine hydrochloride U S P), like quinine, is not curative, but simply controls the acute attack, and if a person succeeds in throwing off the infection, he does so by his own defense mechanism, not as a result of chemotherapy. In one series of cases in Africa, clinical attacks of malaria occurred in 45 per cent of those who were receiving a supposedly adequate prophylactic dose of the drug. The author does not refer to the use of sulfonamide compounds.

*Pleurodynia*—An outbreak of 166 cases of pleurodynia occurred in Brooklyn in July 1943<sup>199</sup>. Either the disease differed in certain respects from that described in previous reports or attention was focused on symptoms previously disregarded. The most important differences were the frequency of pharyngitis (75 per cent of cases) and the evidence of meningoencephalitis, which was noted in 5 adult patients and was characterized by typical clinical signs and symptoms and lymphocytes in the spinal fluid. The prominent symptoms in most cases were the usual ones, namely, fever and severe pain in the upper part of the abdomen or the lower part

196 Penner, L. R. The Possibilities of Systemic Infection with Dermatitis-Producing Schistosomes, *Science* **93** 327-328 (April 4) 1941.

197 Blum, B. B., and Lilga, H. V. Schistosomiasis Infection. Report of Two Cases Found in Northern Michigan, *J. A. M. A.* **121** 125-126 (Jan 9) 1943.

197a Anderson, K. The Cultivation from Granuloma Inguinale of a Microorganism Having the Characteristics of Donovan Bodies in the Yolk Sac of Chick Embryos, *Science* **97** 560-561 (June 18) 1943.

198 Coggeshall, L. T. Malaria as a World Menace, *J. A. M. A.* **121** 8-11 (May 1) 1943.

199 Howard, T., Weymuller, C. A., Edson, J., Ittner, E., Watson, J., and Cassidy, M. Epidemic Pleurodynia in Brooklyn in the Summer of 1942, *J. A. M. A.* **121** 925-929 (March 20) 1943.

of the chest, in both places sufficiently severe to embarrass breathing or to suggest some acute abdominal infection. Convulsions were common in infants. Recoveries were prompt, often within one or two days, but recurrences were common. Aside from pain, which sometimes persisted for weeks there were no sequels.

The third case of human infection with *Pasteurella pseudotuberculosis* in the United States has been reported<sup>200</sup>. The bacterium was isolated from the blood of a patient who recovered from the disease.

The first case of tick paralysis to be reported from the eastern part of the United States occurred in New York in a child of 3<sup>201</sup>. During the course of the disease a partly engorged dog tick was found attached to the scalp. On its removal "the disappearance of the patient's symptoms was most dramatic." It is difficult to understand how so instantaneous a cure is possible.

A puzzling disease known as gin fever, Monday fever, Mill fever or byssinosis has long been noted among employees in cotton mills and among those who inhale the dust of jute, grain, flax and hemp. After hundreds of cases occurred in the summer of 1941, Neal and his co-workers,<sup>202</sup> studying the problem, concluded that a short gram-negative bacillus belonging to the genus *Aerobacter* was the causative agent. It is found chiefly in low grade, stained cotton and is inhaled. The endotoxin it liberates apparently causes disease. The disease begins several hours after exposure with a chill or chilliness, fever, cough, headache, conjunctival irritation and fatigue and lasts four or five days. Intradermal tests with filtrates of the bacillus cause specific hypersensitive inflammatory lesions.

Bradley<sup>203</sup> describes the outbreaks of epidemic nausea and vomiting in several English schools. The disease appeared to be contagious, with an incubation period of two to seven days. The chief symptoms were vomiting, nausea, dizziness, headache and diarrhea. Fever seldom lasted more than twenty-four hours. The disease might be mistaken for food poisoning, but no evidence of the latter was found. All bacteriologic studies gave negative results. An unknown virus was suggested as a possible cause. It may be mentioned in passing that no filtrable virus has ever been incriminated as a cause of gastroenteritis. It is highly probable that some exist that may cause this disease and may account for certain epidemics of so-called dysentery of unknown cause.

Two apparently "new" exanthematous diseases have been reported. In Connecticut, Blake and his associates<sup>204</sup> have studied 11 cases in the last five years. The disease was characterized by fever, no prostration, a reddish brown eruption, general swelling of the lymphatic nodes, splenomegaly and leukopenia with relative lymphocytosis. It occurred chiefly in the spring and fall. The rash appeared from two to fourteen days, usually about six days, after the onset. Chills, chilliness, mild sore throat, conjunctivitis and photophobia were noted at times. All tests for known infections gave negative results.

The other disease was observed in Georgia (and elsewhere) among persons who had bathed a week before in a muddy pool apparently polluted with animal

200 Snyder, G. A. C., and Vogel, N. J. Human Infection by *Pasteurella Pseudotuberculosis*. Report of Case with Recovery, *Northwest Med.* **42** 14-15 (Jan.) 1943.

201 DeSanctis, A. G., and di Sant'Agnese, P. A. Tick Paralysis. Report of a Case in New York, *J. A. M. A.* **122** 86-88 (May 8) 1943.

202 Neal, P. A., Schnitzer, R., and Caminita, B. H. Report on Acute Illness Among Rural Mattress Makers Using Low Grade Cotton, *J. A. M. A.* **119** 1074-1082 (Aug. 1) 1942.

203 Bradley, W. H. Epidemic Nausea and Vomiting, *Brit. M. J.* **1** 309-312 (March 13) 1943.

204 Blake, F. G., Welt, L. G., and Craig, B. Apparently Undescribed Infectious Exanthem, *Yale J. Biol. & Med.* **14** 573-580 (July) 1942.

refuse<sup>201</sup>. Thirty-five cases occurred in August 1940. The onset was sudden, with severe headache, postorbital pain, chilliness and sweating. Lumbar pains, nausea and vomiting, arthralgia and constipation were common. The most striking feature was a fine red measles-like rash chiefly over the anterior aspects of the legs, especially over the tibiae, but noted once on the chest and the abdomen. The exanthem appeared about the sixth day and lasted one or two days. The fever ranged from 100.6 to 104 F, but the pulse was relatively slow. In only 1 case was a swollen lymph node found, an epitrochlear node. The disease lasted about a week. The leukocytes were normal in quantity and quality, and biologic tests for the typhoid group, undulant fever, typhus and tularemia gave negative results. Tests for leptospirosis, or Weil's disease, which I should consider of importance in this instance, were not mentioned, nor was schistosomiasis, although a less likely possibility, discussed. Daniels and Grennan<sup>206</sup> describe a similar disease which they call "pretibial fever," a rather meaningless term which in common parlance means as much as "hot shins" might.

It will be of interest if in both cases the diseases eventually prove to be newly recognized entities or unusual forms of already known infections.

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205 Bowdoin, C. D. A New Disease Entity (?). *J. M. A. Georgia* **31**: 437-438 (Dec.) 1942.

206 Daniels, W. B. and Grennan, H. A. Pretibial Fever. An Obscure Disease, *J. A. M. A.* **122**: 361-365 (June 5) 1943.

## Book Reviews

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**Allergy** By Erich Urbach, M D., with the collaboration of Philip M. Gottlieb, M D. Price, \$12.00 Pp 1073, with 396 illustrations New York Grune & Stratton, 1943

This is a rather exhaustive treatise on clinical allergy, containing most of the orthodox information and arrangements found in a number of other books on this phase of medicine and having, in addition, some of the individualistic views and terminology of the author. The text is divided into three parts. Part 1 deals with the fundamentals of allergy, part 2 discusses the etiologic agents, and part 3 concerns itself with the manifestations and therapy. A large part of the voluminous literature on allergy has been incorporated in the text, for which the specialist and the advanced student in allergy will be grateful. One who has had little practical experience in clinical allergy may become confused by the enormous detail and insufficient evaluation of this material.

A valuable contribution in this book is a complete chapter on allergy with relation to certain infectious diseases. Another feature is the exposition of Urbach's new terminology and classification of the phenomena of hypersensitiveness. He uses the term "pathergy" to designate all altered reactivity. The term allergy or "allergic pathergy" is confined by him to specific altered reaction in which specific antibodies are found. Other terms prominent in the book are "parallergy," "metallergy," "nonallergic pathergy" and "allergization." The concepts represented by these names are not new, although the terminology has been adopted by the author. It is to be regretted that in the chapter on diagnosis the author saw fit to devote only one paragraph to the important phase of history taking. In the chapter on treatment Urbach summarizes his previously published work on "propeptan" treatment, which consists of the use of specific peptones prior to feeding allergenic foods. Although this work has in general failed to receive recognition in this country, it is gratifying to know that the details are available for further experimentation. Urbach favors oral pollen therapy, a stand which would be challenged by American allergists of large experience. Some points in technical details are contrary to accepted ideas. For example, the inference that the allergist should confine himself to ten to twenty scratches at one sitting has no logical background and would if followed, interfere with efficiency in the practice of allergy. The admonition that alcohol must not be used on the skin prior to making scratches has no clinical foundation.

The book is replete with illustrations, mainly photographs, having a total of 396. Many of these are excellent reproductions of various conditions and particularly cutaneous lesions. Nevertheless, on making a careful appraisal of all the illustrations, the reviewer finds that the majority are repetitious, do not possess teaching value or are entirely superfluous. One or two examples may be mentioned. Figure 118 depicts angioneurotic edema due to egg allergy, figure 119, due to fish, figure 341, due to strawberries, figure 342, due to sardines, figure 343, due to acetylsalicylic acid, figure 344, due to enteritis, etc. Figures 328 to 339, inclusive, and other photographs in various portions of the book show patients with urticaria due to various causes, such as strawberries, milk, bacteria, intestinal parasites, enteritis, colitis, dental infection, effort, sweat and mental factors. It certainly would have sufficed to give two or three morphologic variations and merely to mention the various causes.

Although deletion of numerous photographs and reduction in the size would have improved the book, nevertheless, the author and his collaborator have produced a commendable text on allergy and are to be congratulated particularly for their thoroughness. Urbach's "Allergy" will find a place on the shelves of those who have had sufficient experience to evaluate this subject. For others, such as those general practitioners, pediatricians, internists and rhinologists who may have only a secondary interest in allergy, this exposition will probably be too voluminous and complex.

**The Hemorrhagic Diseases and the Physiology of Hemostasis** By Armand J. Quick, M D., Ph D. Price, \$5.00 Pp 340 Springfield, Ill. Charles C. Thomas Publisher, 1942

In 1941 Quick delivered the Beaumont lectures. This book represents an extension and expansion of these lectures and brings up to date the experimental and theoretic aspects of hemostasis. This is the main subject matter of the monograph, but it is most logically correlated with the hemorrhagic diseases and the bleeding tendency in general.

Following the introductory chapter there are six chapters dealing respectively with thrombin, prothrombin, fibrinogen, thromboplastin, blood platelets and anticoagulants. The succeeding six chapters have to do with the clinical manifestations of the diseases which are characterized by a tendency to bleed. The discussion of thrombopenic purpura is noteworthy, and it can be

said that the other chapters on clinical manifestations are excellent. Particularly notable and of extreme value to clinicians, pediatricians and surgeons is chapter 12, which deals with the hemorrhagic diathesis associated with avitaminosis K, obstructive jaundice, biliary fistula and damage to the liver. Chapter 13 is a continuation of the discussion of the same diathesis in which the hemorrhagic diseases of the newborn and toxic sweet clover disease are presented.

For the laboratory worker there is a well organized appendix which outlines the various procedures and technics employed in the study of the hemorrhagic diseases.

The author is well qualified to discuss hemostasis. He is one of the outstanding students of the subject and is widely recognized as an authority. He has presented his work and the work of others clearly and has satisfactorily evaluated the important clinical and laboratory features of the several diseases that he discusses.

It might not be amiss to state that the book itself is an outstanding example of the art of bookmaking. Since an excellent grade of paper has been used, the illustrations are clearcut. The numerous references are printed in relatively large type and can be readily consulted. Altogether, the monograph may be praised most highly, both for its content and for its appearance.

**Urology in General Practice** By Nelse F. Ockerblad, M.D., and Hjalmar E. Carlson, M.D. Price, \$4.00. Pp. 383. Chicago: The Year Book Publishers, Inc., 1943.

Simplification of medical procedure is highly commendable. In this book an attempt has been made, based on almost forty years of experience in the urologic field, to simplify present urologic methods. The procedures outlined are practical and should direct the medical student and the general practitioner to a solution of the more common urologic problems. Little discussion is presented. The advantages and disadvantages of the procedures recommended are not discussed, and no comparison is made between the methods advised and other available procedures. The brevity of the presentation is an aid to quick assimilation, but at times the discussion is so limited that little specific information can be obtained. This is especially true of the section on urologic diagnosis, in which incontinence, uremia and polyuria are discussed. Most of the topics, however, are dealt with concisely and in sufficient detail to be informative. The chapter on the uses and dangers of catheters and sounds is presented in such a way that much assistance can be obtained in the practical handling of these instruments. The section on sterility presents a definite, practical plan for the diagnosis of this condition in either the male or the female. The language used is conversational and frequently nonmedical.

The book is nicely printed and bound and is to be recommended as a quick and practical guide to those not acquainted with the more common urologic methods.

**Whooping Cough** By Joseph H. Lapin, M.D. Price, \$4.50. Pp. 237, with 25 tables and 24 plates. Springfield, Ill.: Charles C. Thomas, Publisher, 1943.

This handsome monograph includes a systematic discussion of whooping cough in all its phases. History, epidemiology, pathology, symptoms, treatment, etc., are thoroughly discussed, and the bibliographies are adequate. The recent work on preventive vaccination is analyzed, and in general the publisher's statement that the book is based on "extensive clinical experience and exhaustive study of the literature" seems to be justified.

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## IMMUNE SERUM THERAPY FOR OROYA FEVER

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BOSTON

No specific treatment has as yet been developed for Oroya fever, the severe and often fatal anemic stage of Carrión's disease. There have been from time to time numerous attempts at immune therapy with serum or transfusions of whole blood from patients convalescing or recovered from various stages of Carrión's disease<sup>1</sup>. There have undoubtedly been many more trials at therapy along these lines than have been published. The few reports available, however, are inconclusive and neither substantiate nor detract from the possibility that such forms of passive immunization may be beneficial in certain cases.

In the field of chemotherapy, arsenical preparations have been tried by certain investigators<sup>2</sup>, but the evidence for any consistent success in this direction has been entirely unconvincing.

The present communication deals with 3 cases of Oroya fever in which hyperimmune rabbit serum containing a high titer of agglutinins for *Bartonella bacilliformis* was given in moderately large intravenous doses. The results obtained, though not entirely conclusive, are thought to be suggestive enough to warrant reporting.

### MATERIALS AND METHODS

*Production of Immune Serum*—In immunizing rabbits against *B. bacilliformis*, the organism responsible for Oroya fever, four strains were used. These originated from four different sources, as follows. The first strain was isolated from the proboscis of a Peruvian sandfly by Dr. Marshall Hertig in 1939. The second originated from a patient with Oroya fever in Peru and was obtained by Dr. Q. M. Geiman in 1939. The third strain was isolated from a patient with severe Oroya fever in Colombia in 1940 and was obtained from Dr. José Jimenez Franco, of Lima. The fourth strain, from a patient with severe Oroya fever in Peru, was isolated by me in 1940.

All of these strains had been maintained in the laboratory on Geiman blood agar and were consistently found to be motile. After five days' incubation at 28 C the growth was washed off the slants with isotonic solution of sodium chloride, centrifuged and resuspended in isotonic solution of sodium chloride. The suspension used in immunizing rabbits consisted of a mixture of equal parts of all four strains, representing a concentration of the growth of two slants per cubic centimeter of suspending medium.

Nine rabbits received from seven to eleven inoculations, three inoculations of 1 cc each being given on three successive days, with rest periods of three to four days between the series of three injections (table 1). The antigen was given intravenously. One animal (rabbit 1533) was immunized with a suspension of formaldehyde-treated organisms of the same basic composition as that given to the remaining animals in the fresh untreated state.

This investigation was financed in part from the Repayments Fund of the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School.

From the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School, and the National Institute of Hygiene and Public Health, Lima, Peru.

1 Odriozola, E. Cong méd latino-am 5 139, 1913. Olachea, A. S. Rev méd peruana 4 412, 1932. Groot, H., Mayoral, P., and Martínez, R. E. Rev Fac de med, Bogotá 9 545, 1941.

2 Manrique, B. Reforma med, Lima, 1937, vol 23. de la Rocha, L. E. Bol Inf de la Asoc med per, 1938, vol 5.



At the end of the total period of immunization, each animal was bled two, or in some instances three, times. The first two bleedings, of 50 cc each, were carried out on the same day, and each was followed by the intravenous administration of 30 cc of 20 per cent solution of dextrose. The third bleeding took place the following day if the animal was scheduled to be bled out for the maximum yield of serum.

Four of the rabbits in the present series (rabbits A, B, 1531 and 1533) had been used in earlier experiments involving immunization with the same four strains of *B. bacilliformis* previously described. The titer which had been obtained for each animal is shown in table 1. This titer, when it was high, had declined somewhat during the six months between the original immunization and that carried out for the present investigation. It is of interest to note that the 5 remaining rabbits (D, E, F, G and H), which had not been previously immunized, produced titers equal to those of the first group of animals.

The titer of the serum from these animals at the end of the period of immunization was consistently high, in most instances agglutination occurring at a final serum dilution, after the addition of the antigen, of 1:2,560. The serum from the 1 rabbit (rabbit 1533) immunized with suspension of formaldehyde-treated organisms agglutinated to a titer as high as did that from the animals immunized with the fresh untreated organisms.

In determining the agglutinating titer of these serums, the agglutination test was performed with a formaldehyde-treated antigen. This antigen consisted of a mixture of the four strains

TABLE 1—*Immunization of Rabbits*

Rabbit Number	First Immunization Highest Agglutinin Titer Obtained	Second Immunization Number of Injections	Total Amount of Suspension Given, Cc	Final Agglutinin Titer (Expressed as Final Dilution of Serum)		
				First Bleeding	Second Bleeding	Third Bleeding
A	1:10	7	14	1:2560		
B	1:160	11	18	1:2560	1:2560	
1531	1:320	11	18	1:640		
1533*	1:320	7	7.5	1:2560	1:2560	1:2560
D	No previous immunization	11	13	1:2560	1:2560	
E	No previous immunization	11	13	1:2560	1:2560	
F	No previous immunization	11	13	1:2560	1:2560	
G	No previous immunization	9	7.5	1:2560	1:2560	
H	No previous immunization	9	7.5	1:2560	1:2560	

\* Immunized with a suspension of formaldehyde-treated organisms.

used in immunizing the animals suspended in a 0.4 per cent solution of formaldehyde U. S. P. in isotonic solution of sodium chloride. The type of flocculus occurring with this antigen when agglutinated with serum from rabbits immunized with live and with formaldehyde-treated organisms, was seen grossly to be fine and flaky. Under the dark field microscope, the organisms were found to be arranged in strands closely interwoven. This was in striking contrast to the appearance of the flocculus produced by agglutination of living organisms by hyperimmune rabbit serum.<sup>3</sup> Here the flocculus was tightly coherent and coarse, and under the dark field microscope the organisms were seen to be tightly clumped. Agglutination occurred at higher dilution of serum with the formaldehyde-treated antigen than with the fresh untreated antigen. The former seems thus to be more sensitive than the latter.

#### REPORT OF CASES

**CASE 1**—A 51 year old foreman, in the employ of an electric power project in the Santa Eulalia valley, was seen at his home, in Lima, on April 12, 1942, complaining of fever, malaise and increasing prostration of eighteen days' duration and deep jaundice of seven days' duration.

**History**—His past history revealed that he had had typhoid in 1900, gonorrhea in 1917 and 1929 and malaria in 1921. There was no history of addiction to alcohol. A native of Lima, his residence in regions where Carrion's disease is endemic had been prolonged but divided into three periods, as follows: 1928-1929, Autisha, 1934 to 1938, Callahuanca and Barbablanca, 1938 to 1942, Autisha. In the intervening periods, he had lived in Chosica, Huancavelica, Lima

and Cuzco, in none of which localities Carrion's disease is known to occur. At no time had he had any severe illness, unexplained fever, jaundice or eruption of any kind. It was assumed therefore, that, although he had had prolonged exposure in the endemic regions of the Santa Eulalia valley, he had never contracted clinical Carrion's disease in any form. He had been seen by me on March 10, 1942 in Autisha, at which time he was in good health. Cultures of blood taken on that date showed no growth of organisms, agglutination tests with *B. bacilliformis* gave negative reactions in all dilutions, the hemoglobin content was 11 Gm per hundred cubic centimeters, and organisms were not seen in the blood film.

The patient had remained asymptomatic until March 25, when he was taken with a sudden chill, with malaise, and with sweating and a temperature of 104 F. For the ensuing eleven days, during the last nine of which he was in Lima, his temperature had been noted to be only slightly elevated. From April 5 to April 9, he had again been in Autisha. A blood count done on April 7 had shown the erythrocytes to number 4,600,000 per cubic millimeter and the leukocytes 7,000 per cubic millimeter with a normal differential count, *B. bacilliformis* had not been observed in a careful examination of the blood films.

On April 5, he had noted the sudden appearance of jaundice, which day by day increased in intensity. His urine had become coffee colored, the stools had remained normal in color, and

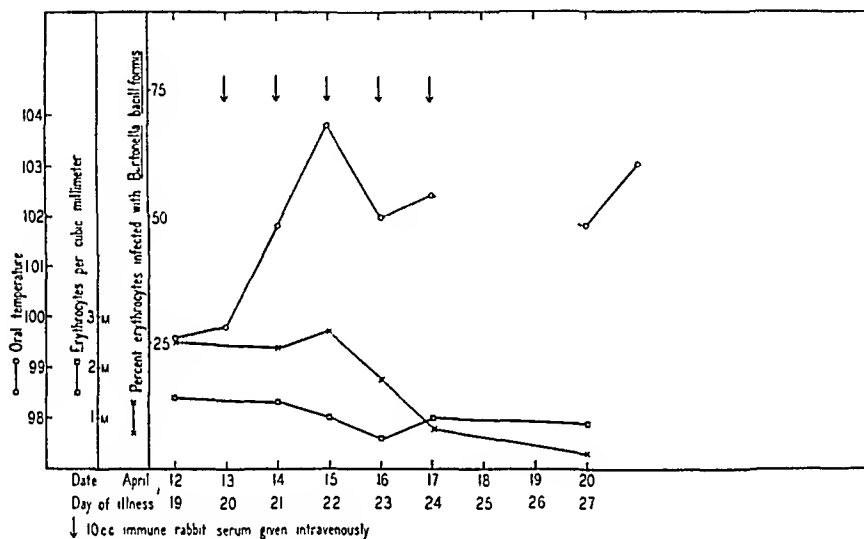


Fig 1 (case 1) —Course of the disease in a case of treated Oroya fever

TABLE 2—Laboratory Data in Case 1

Date	Day of Disease	RBC	WBC	Hb, Gm	RBC Infected, %	Hematocrit	Blood Cultures	Agglutination Test, Final Dilutions of Serum							
								1 2	1 10	1 20	1 40	1 80	1 160		
March 10				11	0		—	0	0	0	—	—	—		
April 7	14	4,600,000	7,000		0										
April 12	19	1,400,000	9,800	5.0	25	23	+	4	1	0	—	—	—		
April 14	21	1,300,000	8,700	4.0	24	12	+	4	3	2	0	0	0		
April 15	22	1,000,000		3.5*	27		+	4	4	3	2	1	0		
April 16	23	600,000		3.5*	18		+								
April 17	24	1,000,000		3.6*	8		+	4	4	3	3	2	0		
April 20	27	900,000	5,900	3.5	3	12	+	4	4	3	2	1	0		
June 6	47						+								

	Blood Chemistry, Gm per 100 Ce			Urinalysis		
	Total Protein	Albumin	Globulin	Protein	Urobilin	Sediment
April 17	6.6	2.9	3.7	Slight trace	4 plus	Not remarkable

\* Determination obtained on electric photocolorimeter

he had vomited two or three times a day during the ensuing week. On April 12 I saw him for the second time, in Lima, where he had been confined to bed for three days.

*Physical Examination*—The only significant conditions observed on physical examination were a temperature of 104 F, severe jaundice, moderate dehydration, an enlarged liver (palpable 3 fingerbreadths below the right costal margin) and a moderately loud systolic murmur at the apex.

The laboratory data are summarized in table 2. It is noteworthy that in five days (April 7 to April 12) the red blood cell count had fallen to 1,400,000 per cubic millimeter and the hemoglobin content to 5 Gm per hundred cubic centimeters and that on April 12 *B. bacilliformis* was seen for the first time, in 25 per cent of the erythrocytes.

*Subsequent Course*—The patient's temperature remained elevated during the ensuing week (fig 1), and he continued to complain of extreme malaise, anorexia, insomnia and occasional nausea and vomiting. The jaundice had diminished noticeably by the end of the week. The patient improved slowly, and he was reported on August 12 to be well on the way to recovery. No eruption had appeared up to that time.

*Treatment*—During the acute stage of his illness, the patient was treated with parenteral injections of vitamin B complex and liver extract. He was also given a total of 50 cc of

TABLE 3—Laboratory Data in Case 2

Date	Day of Disease	RBC	WBC	Hb, Gm	RBC Infected, %	Hematoerit	Blood Cultures	Agglutination Test, Final Dilutions of Serum					
								1 2	1 10	1 20	1 40	1 80	1 160
April 2	6	600,000	14,000	25	6	9	+	4	4	1	0	-	-
April 5	8	900,000	14,900	26	68								
April 7	10	900,000	12,400	35	20	11	+	4	4	2	0	-	-
April 8	11	1,300,000	9,700	10	16	12	+	4	4	4	-	-	-
April 9	12	900,000	7,800	38	4								
April 10	13	1,200,000	4,900	15*	1	16	+	4	4	4	-	-	-
April 11	14	1,400,000	6,800	4	0	17	+	4	4	4	3	0	-
April 12	15	1,800,000	10,800	-	-			-	-	-	-	-	-
April 13	16	1,900,000	12,000	53	0	20	+	4	4	4	-	-	-
April 14	17	1,400,000	7,300	13	0	18	+	4	4	4	2	1	0
April 15	18	1,500,000		18		17	+	4	4	4	2	1	0
April 16	19	1,500,000		55				4	4	1	3	2	0
April 20	23	1,700,000	10,000	55		22	+	4	4	3	2	1	
May 18							+						
June 5		3,600,000	9,800										

Blood Chemistry, Gm per 100 Cc			
Total Protein	Albumin	Globulin	
April 20	6.0	3.4	2.6

\* Determination obtained on electric photocolormeter.

hyperimmune rabbit serum in intravenous doses of 10 cc each on the twentieth through the twenty-fourth day of his illness (fig 1). There was no untoward reaction, and an intradermal test before the administration of each dose invariably gave a negative result.

**CASE 2**—A 15 year old native of the village of Vilcabama, in the Department of Apurimac was seen in the Hospital Dos de Mayo in Lima on April 3, 1942, two days after his admission.

*History*—The patient had lived in his native village, where no verruga is known to occur, until nine months prior to admission to the hospital, at which time he had gone to Cuzco. Here he had remained for six months, and he had then made his way to Lima via Ayacucho, Huancayo and the Rimac valley. The trip from Huancayo to Lima, including passage through the verruga zone, had been made in one day and one night. He had arrived in Lima for the first time three months prior to his admission to the hospital, his only exposure to infection up to that point having occurred during the night of travel, previously alluded to, through the lower Rimac valley. One month prior to admission, the patient had gone up the Rimac valley as far as Matucana, the upper limit of the verruga zone, stopping at different points on the way up and back seeking work. Eight days were spent in thus traversing the verruga zone, and the patient returned to Lima twenty-eight days prior to admission, on March 4. Three days prior to admission, on March 29, he was seized with a sudden chill, severe febrile symptoms, headache and extreme malaise. Three days later, on April 1, he was admitted to the hospital because of exhaustion and inability to work, with fever and extreme weakness.

*Physical Examination*—Moderate icterus was evident. The mucous membranes were extremely pale, and the patient was perspiring profusely and complaining of shortness of breath. The lungs were clear to auscultation and were resonant throughout. Over the apex of the heart there was heard a moderately loud systolic murmur. The liver and spleen were not palpable. There were a few small cervical lymph nodes which were slightly enlarged and not tender. Physical examination yielded otherwise unremarkable results.

The laboratory data are summarized in table 3.

*Subsequent Course*—The patient's course was at first only moderately febrile. Later, however, he had an irregular fever, the temperature ranging from 100 to 103 F (fig 2). At no time did he feel desperately ill. On the fourteenth day of his illness, he was discovered to have the beginning of a sudaminal eruption, characterized by pale nodules 1 to 2 mm in diameter, which appeared first over the right wrist and lower part of the forearm. Within five or six days this eruption had spread over the chest and abdomen, and by the twenty-first day of the disease it had spread in miliary form over the entire trunk and over all four extremities. A specimen of the skin over the right wrist at the point where the eruption had first appeared was taken for biopsy, but nothing characteristic was seen on section of the specimen. About one month later, there was found at the site of the biopsy specimen a larger typical verruga nodule, about 1 cm in diameter. On the thirtieth day of the disease, the verrucous eruption became secondarily infected, with the appearance of oozing impetiginous lesions over most of the body. As this superimposed infection subsided during the ensuing two

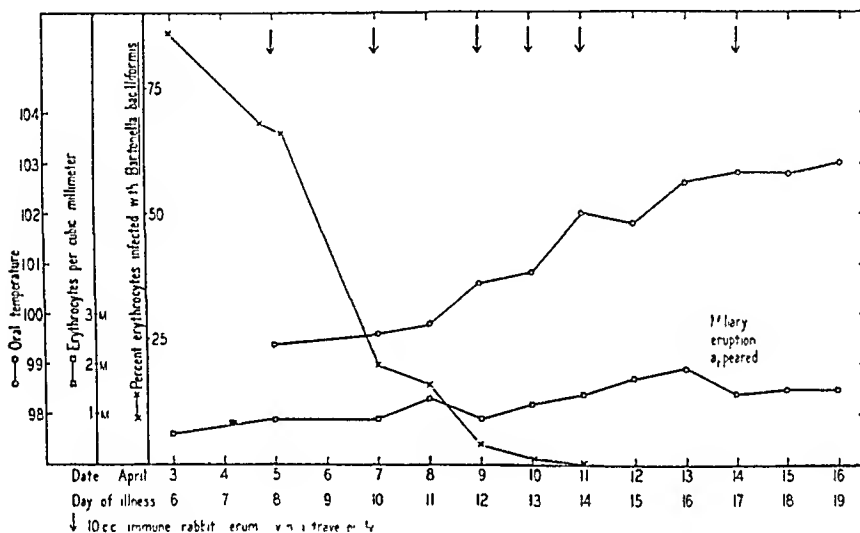


Fig 2 (case 2)—Course of the disease in a case of treated Oroya fever

weeks, the miliary verruga lesions again became visible as red spots on the skin. By about the seventh week of the disease, that is five weeks after the appearance of the verruga eruption, signs of eruption had almost completely subsided. The patient was reported to be in good health at that time. He was discharged from the hospital and has not been heard from since then, hence no long term follow-up has been possible.

*Treatment*—Along with minimal nonspecific supportive therapy, this patient received a total of 60 cc of hyperimmune rabbit serum (fig 2). This was administered in intravenous doses of 10 cc each on the eighth, tenth, twelfth, thirteenth, fourteenth and seventeenth days of the patient's illness. There were no untoward reactions, and an intradermal test before each dose of serum invariably gave a negative reaction.

**CASE 3**—A 21 year old member of a military detachment, a native of Ayacucho, was seen at the military hospital of San Bartolome, in Lima, on April 13, 1942. His past history was unremarkable except for his having had typhus in childhood.

*History*—The patient had completed a tour of duty at Chunchipe, on the Ecuadorian frontier, from July 1941 to Feb 28, 1942. During the first week in March 1942, he had gone to Chanchaqui, between Piura and Huanaco, where verruga is not known to occur, and he had returned to Lima by March 6, 1942. On March 9, he had left Lima for Ayacucho and had been delayed between the hours of 4 and 8 p m on March 10, at Huanta, in the endemic region, by a landslide which had blocked the road. He had arrived in Ayacucho on March 11, had stayed there until March 24 and had returned to Lima on March 25. At noon on March 23 he had been taken with a sudden chill, complaining of headache, malaise, "fever" and

articular pains The next morning he had vomited once During the next few days, his symptoms had continued, with chilly sensations, irregular afternoon fever and ten to twelve diarrhetic bowel movements without blood or mucus He had been admitted to the hospital on March 25

*Physical Examination*—When seen for the first time by me, on April 13, the patient was extremely pale and weak, was sweating profusely and had pronounced edema of the face and of both lower eyelids There was severe scleral icterus He had had several profuse nosebleeds during the day, which had been arrested by tight packing of the anterior and posterior nasal passages The temperature was 102.6 F, the pulse rate 108 and the respiratory rate 16 A few small cervical glands were palpable The lungs were resonant and clear to auscultation throughout, and the heart was not remarkable The liver and spleen were not made out, and there was no evidence of fluid in the abdomen The physical examination otherwise revealed unremarkable conditions

The laboratory data are summarized in table 4

*Subsequent Course*—The patient had a sustained fever during most of the short time (fig 3) he was being followed by me On the twenty-eighth day of his disease, his tempera-

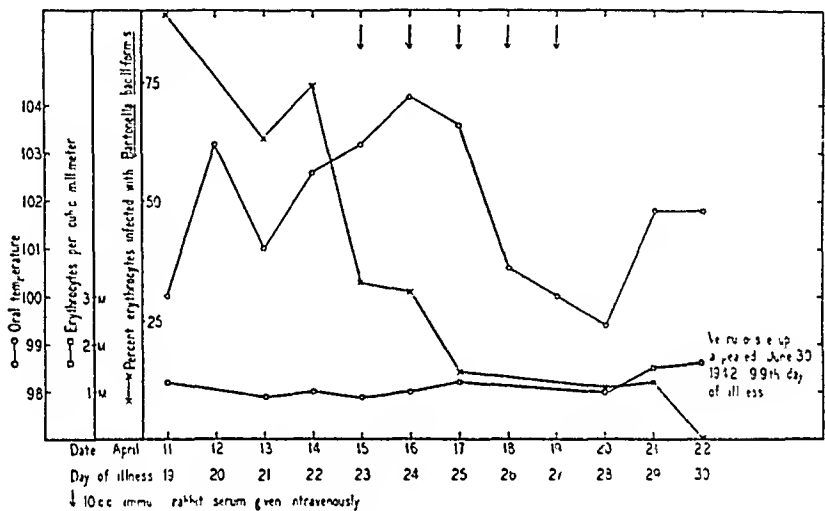


Fig 3 (case 3) —Course of the disease in a case of treated Orova fever

TABLE 4—Laboratory Data in Case 3

Date	Day of Disease	RBC	WBC	Hb, Gm	RBC In field, %	Hemato- crit	Blood Cul- tures	Agglutination Test Final Dilutions of Serum							
								1 2	1 10	1 20	1 40	1 80	1 160		
April 11	19	1,200,000	5,400	3.8	89	15									
April 13	21	900,000	13,200	3.3	63	10	±	3	1	0	-	-	-		
April 14	22	1,000,000	10,200	2.8	71	12	--	4	2	0	0	0	0		
April 15	23	900,000		3.0	33	10	+	4	4	3	2	0	-		
April 16	24	1,000,000		2.7*	31		±								
April 17	25	1,200,000		3.0	14		--	1	4	3	3	1	0		
April 18	26							4	4	4	3	2	0		
April 20	28	1,000,000	4,300	3.5	11	12	+	4	4	4	3	3	1		
April 21	29	1,500,000	9,400	5.0	12										
April 22	30	1,600,000	14,600		0										
May 18	56							0	0	0	0	0	0		

Blood Chemistry								Bleeding Time, Min	Clotting Time, Min
Serum Bilirubin, Mg per 100 Cc	Icteric Index	Total Protein, Gm per 100 Cc	Albumin Gm per 100 Cc	Globulin Gm per 100 Cc					
April 11	3						4	6	
April 13		15							
April 14		12							
April 17		6	6.0	3.4	2.6				
April 21		4							

\* Determination obtained on electric photocolormeter

ture was 99.4 F. On the twenty-fourth day, he was found to have pronounced and painful swelling of the neck at the angle of the jaw bilaterally, greater on the left than on the right. This condition was thought to represent an acute cervical adenitis. The patient's diarrhea continued intermittently, without blood or mucus. There was tenderness over the course of the large bowel, without any spasm of the abdominal wall. By the twenty-ninth day, the swelling in the neck had subsided and become less painful. The diarrhea was ascribed to a possible typhoid or paratyphoid infection, and the patient's serum was found to agglutinate *Eberthella typhosa* to a dilution of 1:500.

During the subsequent two months, the patient's condition was reported to have run a febrile course, he was said to have exhibited signs of what may have been mild peripheral neuritis, which subsequently subsided completely. His anemia improved gradually, with only minimal supportive therapy, and by mid-July his red blood cell count was reported to have reached 3,000,000, with no organisms having been seen on smear since April 22, the thirtieth day of his illness.

On June 30, the ninety-ninth day of his disease, a typical eruption, consisting of scattered pea-sized verrugas on the face and extremities, is reported to have developed. His general improvement was steady thereafter, and he left the hospital in August, about four months after the onset of his illness, still with definite eruption present.

*Treatment*—On the twenty-first and twenty-sixth days of his illness, the patient received transfusions of whole blood, of 100 and 150 cc respectively. This blood had been taken from donors who had denied having had Carrion's disease in the past. From the twenty-third to the twenty-seventh day inclusive, the patient received five daily intravenous doses, of 10 cc each, of hyperimmune rabbit serum, without untoward reaction (fig. 3), an intradermal test prior to each dose invariably gave a negative reaction. Further supportive treatment was minimal.

#### DISCUSSION

In none of these 3 cases was the actual clinical picture dramatically altered by the administration of specific immune rabbit serum. The only point worth noting in this connection is the early appearance of the typical miliary eruption (on the fourteenth day of illness) in the second case, in which invasion of the blood stream was severe (fig. 1). The usual course of events in untreated severe Oroya fever is for the eruption to appear some weeks or months after the acute hemolytic infection of the blood stream has subsided. In this case, the eruption appeared shortly after the number of parasitized erythrocytes had been reduced below a level at which they were easily detectable by microscopic examination of the blood film, although cultures of the blood contained organisms for some time thereafter. The changes in the blood picture in these 3 cases were more striking.

In all 3 cases, measurable diminution in the percentage of infected erythrocytes began simultaneously with or shortly after the institution of serum treatment (figs. 1, 2 and 3). This reduction was real, not apparent, since the red blood cell count remained stationary or even rose slightly while the percentage of parasitized cells fell precipitously. Whether this change was pure coincidence or whether the immune serum administered was partially or wholly responsible for the rapid changes cannot be determined at present. There are two pieces of circumstantial evidence which lend support to the belief that this passive immunization may have hastened the process of reducing the degree of invasion of the blood stream.

The first of these lies in a comparison of the course of the disease in these cases with serum treatment with the natural course of events in cases of Oroya fever in which the patient survived wholly without treatment of any kind. In figure 4 are charted the percentages of infected erythrocytes determined on successive days for several patients from Colombia with Oroya fever. The gradual reduction in the number of *B. bacilliformis* organisms visible on direct smear of blood from these patients took place over a definitely longer period than in the cases herein

reported It is not impossible that this difference may represent the favorable effect of passive immunization

The second piece of evidence which suggests that immune serum has some effect on organisms circulating in the blood stream lies in certain changes noted in the appearance of the growth in cultures of blood taken on successive days, including those on which serum was administered In all 3 cases, the colonies of organisms as seen in German semisolid medium in the first blood culture taken before institution of therapy were finely granular and exceedingly numerous As each dose of serum was given, colonies in serial blood cultures became strikingly different in appearance, those in the later cultures being very much larger and coarser than those in earlier cultures In figure 5 are shown first transfers from cultures of blood taken, in each case, before serum was given and after completion of serum therapy It is of interest that even in as many as three successive transfers from original cultures the difference in morphology previously described was retained in striking manner What this definite change in morphology, possibly brought

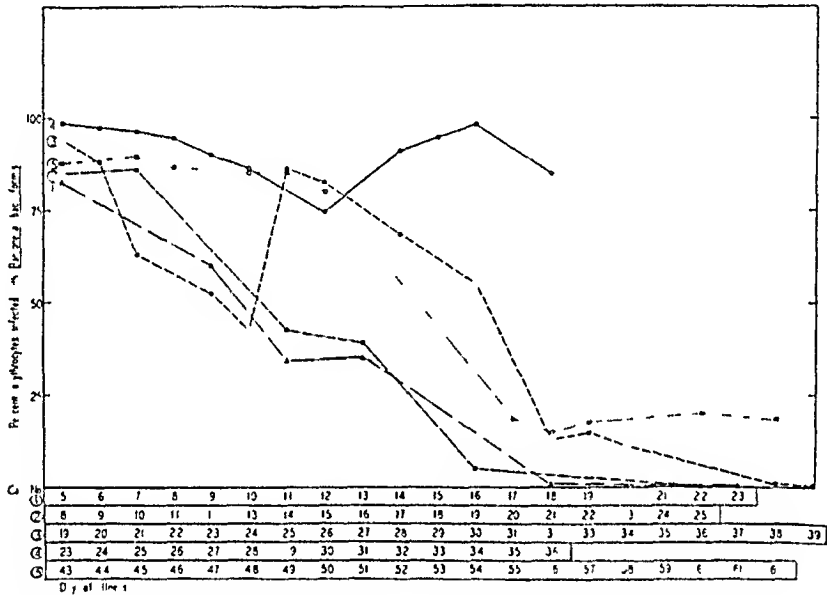


Fig 4—Infection of erythrocytes during the course of untreated Oroya fever (5 cases from Colombia)

about by passive immunization, signifies is not clear One can only speculate on the possibility that it may represent a change in antigenic character, such as a transformation of a smooth to a rough type of growth or from a motile to a non-motile state

At any rate, there are indications, as seen in the reduction of visible infection of erythrocytes and in changes in number and morphology of colonies in the blood cultures, that specific immune serum does have some effect toward clearing the blood stream of organisms A stronger serum might prove to be more completely effective in this regard

The other laboratory data taken during the acute phase, in which the serum was given in each instance, showed no striking changes other than those associated with the gradual and slow general improvement which took place The severe anemia showed little if any improvement in the absence of the usual supportive therapy, which was here entirely unobtainable The titer of agglutinins had at first

been low in each case, as is usual in severe Oroya fever in its early stages. The sudden rise in titer of agglutinins is, of course, explainable by the administration of immune rabbit serum.

In the first case only were there significant changes in blood chemistry, namely a reversal of the serum albumin-globulin ratio and a strong indirect van den Bergh reaction. Damage to the liver was further suggested in this patient by the presence of jaundice more intense than that usually seen in Oroya fever, urobilin in the urine



Fig 5—First transfers from blood cultures before (tube on left) and after (tube on right) serum therapy. Small white colonies are seen suspended in semisolid agar medium. Top tubes, case 1, middle tubes, case 2, bottom tubes, case 3.

and a definitely enlarged liver. There may have been other factors at work here, besides the direct effect of a relatively severe degree of rapid hemolysis, although the patient had denied having had jaundice previously and having used alcohol extensively. Extensive hepatic damage, on the other hand, is known to occur frequently in severe Oroya fever,<sup>4</sup> and this adds the effects of an obstructive mechanism to the hemolytic jaundice already present.

4 Battistini, T. S. Personal communication to the author.



## SUMMARY AND CONCLUSIONS

Immune serum of high agglutinin titer was produced in rabbits by the intravenous administration of large amounts of *B. bacilliformis*, both in the fresh and in the formaldehyde-treated state. The titer obtained in rabbits inoculated with treated organisms was as high as that in animals inoculated with the untreated organisms.

Three cases of severe Oroya fever are reported in detail.

There was no dramatic change in the clinical picture in any of these cases as a result of immune serum therapy, except for the prompt appearance of the typical eruption in case 1. In this case, the time at which the eruption appeared was earlier in the course of the disease than is usual in untreated Oroya fever. This occurrence is as yet unexplainable.

It is thought that in these cases intravenous administration of immune rabbit serum may have caused an appreciable diminution in the percentage of erythrocytes infected with *B. bacilliformis*, as determined by examination of blood films. A comparison is made of these cases with 5 cases of severe untreated Oroya fever from Colombia. The reduction of visible erythrocyte infection appears to be much more gradual in these cases than in those in which immune serum was used in treatment.

Administration of immune serum in the 3 cases herein reported caused a diminution in the number of colonies of organisms obtained in serial blood cultures taken during the period of treatment. The type of colonies obtained in cultures taken before and after administration of serum indicated a change from finely granular and diffuse growth to a coarse and sparsely scattered type of growth. These changes are retained in transfers from original blood cultures, and their significance is not clear.

Dr Telemaco S. Battistini, Director of the National Institute of Hygiene and Public Health, in Lima, Peru, provided laboratory space for the portion of this investigation carried out in Peru. Drs E. E. Tyzzer, A. W. Sellards and Q. M. Geiman, of the Department of Comparative Pathology and Tropical Medicine of the Harvard Medical School, made available extensive facilities for the preparation of materials used in the course of this work. Drs Carlos Protzel and Jose Jimenez Franco, of the Hospital Dos de Mayo, Dr Guillermo Ricketts Rev. de Castro, of the military hospital of San Bartolome, and Dr Victor Palti gave permission for the detailed study of the 3 cases herein reported. Dr Hernando Groot, of Bogota, supplied the data on the 5 cases of Oroya fever from Colombia.

# RELATION BETWEEN HEPATIC AND PLASMA CONCENTRATIONS OF VITAMIN A IN HUMAN BEINGS

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To recognize clinical and subclinical vitamin A deficiency the blood level of vitamin A,<sup>1</sup> visual tests for night blindness,<sup>2</sup> biomicroscopic changes in the cornea<sup>3</sup> and other means have been used. The results obtained and the conclusions drawn have varied. Some authors have concluded that vitamin A deficiency is common<sup>4</sup>, others have considered it to be rare<sup>5</sup>.

The liver is the main storage place for vitamin A. It contains about 95 per cent of the total amount of the vitamin in the body<sup>6</sup>. Therefore, it can serve as an index of the vitamin A status. Hence, it would seem that those tests for deficiency of the vitamin would be significant which parallel low or absent stores in the liver.

The present study deals with the significance of the vitamin A level of the blood. The vitamin A concentration of human blood plasma was compared with the vitamin A content of biopsy specimens of the liver in continuation of previously reported studies.<sup>7</sup> In addition, the histologic distribution of vitamin A in the specimens of

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1 (a) Schneider, E, and Widmann, E. *Klin Wchnschr* **14** 670, 1935. (b) Clausen, S W, and McCoord, A B. *J Pediat* **13** 635, 1938. (c) Steininger, G, Roberts, L J, and Brenner, S. Vitamin A in the Blood of Normal Adults, *J A M A* **113** 2381 (Dec 30) 1939. (d) Lindqvist, T. *Acta med Scandinav (supp)* **97** 1, 1938. (e) Kimble, M S. *J Lab & Clin Med* **24** 1055, 1939.

2 (a) Jeans, P C, Blanchard, E, and Zentmire, Z. Dark Adaption and Vitamin A, *J A M A* **108** 451 (Feb 6) 1937. (b) Hecht, S, and Mandelbaum, J. Relation Between Vitamin A and Dark Adaption, *ibid* **112** 1910 (May 13) 1939, *Am J Physiol* **130** 651, 1940. (c) Feldmann, J B. Instrument for Determining Course of Dark Adaption and for Measuring Minimum Light Threshold, *Arch Ophth* **12** 81 (July) 1934. (d) Young, G, and Wald, G. *Am J Physiol* **131** 210, 1940. (e) Isaacs, B L, Jung, F T, and Ivy, A C: Vitamin A Deficiency and Dark Adaption, *J A M A* **111** 777 (Aug 27) 1938.

3 Kruse, H D. *Milbank Mem Fund Quart* **19** 207, 1941.

4 Corlette, M B, and Youmans, J B. *Am J M Sc* **195** 54, 1938. Jeghers, H. Degree and Prevalence of Vitamin A Deficiency in Adults, *J A M A* **109** 756 (Sept 4) 1937. Stiebeling, H K, and Phipard, E F. Diets of Families of Employed Wage Earners and Clerical Workers in Cities, Circular 507, United States Department of Agriculture, 1939.

5 Hunt, E P. *Milbank Mem Fund Quart* **19** 252, 1941. Hecht and Mandelbaum<sup>2b</sup>.

6 (a) Moore, T. *Biochem J* **25** 275, 1931. (b) Baumann, C A, Rusing, B M, and Steenbock, H. *J Biol Chem* **107** 705, 1934.

7 Meyer, K A, Popper, H, Steigmann, F, Walters, W H, and Zevin, S. *Proc Soc Exper Biol & Med* **49** 589, 1942.

liver was studied by fluorescence microscopy. As previously shown,<sup>8</sup> this distribution varies greatly in normal and more in pathologic conditions. Consequently, the distribution of vitamin A was compared with the plasma and liver levels in order to understand better their relationship. At the same time a comparison between the histologic and the chemical methods was made.

In the course of this investigation additional data concerning vitamin A metabolism were collected, such as (a) the influence of anesthesia, (b) the results of feeding huge doses of the vitamin, and (c) the concentration of carotene in the plasma and in the liver.

The vitamin A content of the livers of rats has been compared with the vitamin A content of the blood by several investigators. Some investigators assumed a close parallelism between the vitamin in the liver and that in the blood<sup>9</sup>, others have failed to find it,<sup>10</sup> the results apparently depending on the experimental condition of the rats. Some relation between the vitamin A content of the blood and that of the liver has been found by Lewis, Bodansky and Haig<sup>11</sup> in infants studied post mortem. Our own examinations<sup>7</sup> of adults revealed parallelism only in certain conditions. To similar conclusions came Stewart and Rourke<sup>12</sup>.

That the relation between blood and liver concentrations of vitamin A in human adults is not simple is brought out by extensive chemical<sup>13</sup> and histologic<sup>8b</sup> examinations, which failed to show absence of vitamin A in any adult human liver. This speaks against the common occurrence of subclinical vitamin A deficiency in human beings. These contrasting results can be explained only by disturbances in the release of vitamin A from the liver, a possibility already suspected by Nylund and With<sup>14</sup> in 1941.

#### MATERIAL AND METHODS

The principal study concerns 76 patients operated on for conditions in the upper part of the abdomen (disease of the gallbladder, carcinoma of the stomach, peptic ulcer or carcinoma of the biliary tract and pancreas). The hepatic function was investigated by several procedures described in another paper<sup>15</sup>.

Because of studies reported,<sup>16</sup> some of the patients received 75,000 U S P units of vitamin A<sup>17</sup> orally several days before operation. In all of them the vitamin A of the plasma

8 (a) von Querner, F. *Klin Wchnschr* **14** 1213, 1935. (b) Popper, H. *Histologic Distribution of Vitamin A in Human Organs Under Normal and Under Pathologic Conditions*, *Arch Path* **31** 766 (June) 1941, *J Mt Sinai Hosp* **7** 119, 1940, *Proc Soc Exper Biol & Med* **43** 234, 1940. (c) Meyer, K A., Popper, H., and Ragins, A B. *Histologic Distribution of Vitamin A in Biopsy Specimens of Liver*, *Arch Surg* **43** 376 (Sept) 1941.

9 Lewis, J M., Bodansky, O., Falk, K G., and McGuire, G. *Proc Soc Exper Biol & Med* **46** 248, 1941, *J Nutrition* **23** 351, 1942. Horton, P B., Murrill, W A., and Curtis, A C. *J Clin Investigation* **20** 387, 1941.

10 Brenner, S., Brookes, M C H., and Roberts, L J. *J Nutrition* **23** 459, 1942. McCoord, A B., and Luce-Clausen, E M. *ibid* **7** 557, 1934. Leong, P C. *Biochem J* **35** 806, 1941. Josephs, H W. *Bull Johns Hopkins Hosp* **71** 253, 1942.

11 Lewis, J M., Bodansky, O., and Haig, C. *Level of Vitamin A in the Blood as an Index of Vitamin A Deficiency in Infants and Children*, *Am J Dis Child* **62** 1129 (Dec) 1941.

12 Stewart, J D., and Rourke, G M. *Surgery* **11** 939, 1942.

13 Moore, T. *Biochem J* **31** 155, 1937.

14 Nylund, C E., and With, T K. *Acta med Scandinav* **106** 202, 1941.

15 Meyer, K A., Steigmann, F., Popper, H., and Walters, H W. *Influence of Hepatic Function on Metabolism of Vitamin A*, *Arch Surg* **47** 26 (July) 1943.

16 Popper, H., Steigmann, F., and Zevin, S S. *J Clin Investigation*, to be published.

17 The product used was a vitamin A ester concentrate containing 200,000 U S P units of the vitamin per gram, furnished by Distillation Products, Inc. of Rochester, N Y. This was diluted with corn oil to contain 37,500 U S P units per cubic centimeter.

had returned to a constant level before operation. To vary the nutritional status of the patients, 7 received three to seven daily doses of 500,000 U S P units of the vitamin, which was discontinued several days before the operation. The vitamin in the blood had returned to a constant level before operation. In 51 patients the plasma content of vitamin A was determined before, during (immediately after the specimen of liver was taken for biopsy) and one hour after the operation.

To illustrate the ranges of the preliminary (before any vitamin A was given) vitamin A levels in our material, the plasma levels of the 167 subjects studied are shown in table 1.

The vitamin A level of the plasma was determined by the Carr-Price reaction. The extractions were made according to the method of Kimble<sup>18</sup> from 4 cc of plasma (in only a few cases from 2 cc). The purified benzene (petroleum ether) extracts were colorimetrically estimated for the concentration of carotene by potassium dichromate standards or by the photoelectric colorimeter. The calibration in both instances was done with pure crystalline beta carotene<sup>19</sup> in purified benzene. The readings for vitamin A were made in the majority of the cases with copper sulfate solutions according to a modification of Josephs' method<sup>19</sup>, in some cases the photoelectric colorimeter of Sheard and Sanford was used. The two methods checked satisfactorily (for 100 samples both methods were used, with maximal differences of 6 micrograms in levels below 100 micrograms per hundred cubic centimeters and 24

TABLE 1—*Vitamin A and Carotene Levels of the Plasma in the Material Studied (Preliminary to Any Vitamin A Administration or Operation) Grouped According to Disease and Sex*

Diagnosis	Plasma Vitamin A Level in Micrograms per 100 Cc								Average Plasma Carotene Level in Micrograms per 100	
	Males				Females					
	No of Cases	Maximum	Minimum	Average	No of Cases	Maximum	Minimum	Average		
									Males	Females
Hernia and fracture	10	48	19	33					64	
Peptic ulcer	27	111	3	34	1			43	49	112
Miscellaneous diseases	16	55	2	30					51	
Gallbladder disease without jaundice	3	38	20	27	24	66	17	34	68	49
Postinfectious condition	5	37	6	20					35	
Carcinoma of gastrointestinal tract	16	44	0	18.5	2			19.5	61	17
Obstructive jaundice	14	16	0	4.0	4	17	0	7	94	51
Acute hepatitis	9	11	0	4					57	
Cirrhosis of the liver	18	35	0	9	6	22	0	8	59	98
Vitamin A deficiency and sprue					2	0	0	0		9
Diseases of the kidney	8	210	14	84					79	

micrograms in levels from 100 to 500 cc.) For the reading with copper sulfate standards the following steps were taken. The residue of the extract after evaporation of the purified benzene was taken up in 1 cc of chloroform, 0.1 and 0.2 cc of the chloroform solution were each transferred with a micropipet to test tubes of the same size as the standards. One-tenth cubic centimeter of chloroform was added to the test tube containing 0.1 cc of chloroform extract, and then to each tube 1 cc of a saturated solution of antimony chloride was added and a comparison was made immediately with the copper sulfate standards, the maximum color, which fades in a few seconds, being utilized. If the color with 0.1 or 0.2 cc was too weak, a greater aliquot of the original chloroform solution was reduced by evaporation to 0.2 cc for the reading. In each determination, readings of at least two concentrations were made, which had to check. For the photoelectric colorimeter 0.3 cc of the chloroform extract was transferred to microcells and 1.8 cc of antimony trichloride was added immediately before reading.

The copper sulfate standards and the photoelectric colorimeter were calibrated with chloroform solutions of two batches of crystalline vitamin A alcohol<sup>20</sup>. Since crystalline vitamin A is not stable in chloroform solution, probably because of ultraviolet irradiation,<sup>21</sup> care was taken to calibrate within twenty minutes after the crystals were dissolved in chloroform. During this interval, no appreciable loss of vitamin A was found by the Carr-Price reaction.

18 Received from the S. M. A. Corporation, Chagrin Falls, Ohio.

19 Josephs, H. W. Bull. Johns Hopkins Hosp. 65:112, 1939.

20 Supplied by Distillation Products, Inc., Rochester, N. Y.

21 Embree, N. D. Indust. & Engin. Chem. 13:144, 1941.

A second calibration was done with crystalline vitamin A in chloroform solution to which were added liver oils obtained from young rats kept on a vitamin A-deficient diet for twenty-seven days after weaning. The extracts were made by treating the livers as for vitamin A assay, to be described later. No appreciable difference was encountered in the calibration curves (fig 1). The results are reported in micrograms per hundred cubic centimeters of plasma. The conversion factor of microgram to units is 3.28,<sup>22</sup> as we also found in determining three batches of vitamin A concentrates containing 200,000 U S P units per gram.<sup>20</sup> For 36 patients duplicate determinations checked satisfactorily. For some of them, these duplicates were made only with 2 cc of plasma.

After removal of grossly apparent capsule or vessels from the liver, biopsy specimens consisting of 0.1 to 0.4 Gm of liver were saponified in double the amount of a 20 per cent aqueous solution of potassium hydroxide for forty-five minutes in a boiling water bath according to the method of Skurnik and Suhonen.<sup>23</sup> The hydrolysate was treated like the plasma, as previously described after addition of an equal volume of water. Occasionally the chloroform solution was diluted several times before the reading, to bring it into the range of the copper sulfate standards or the calibration curve. The hepatic concentration is recorded as micrograms per gram of fresh liver.

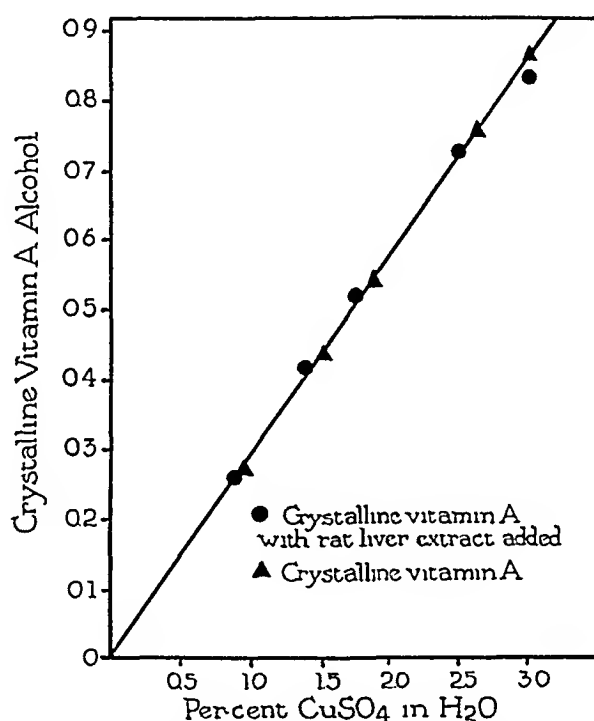


Fig 1—Calibration curve of copper sulfate solutions by chloroform solution of crystalline vitamin A with and without added liver oils obtained from vitamin A-deficient rats

The saponification of blood is a moot question, since during saponification substances other than vitamin A may be liberated or destroyed, which might increase, reduce or interfere with the development of the Carr-Price reaction. In our experience in 45 cases, saponification of the plasma made no difference in values above 30 micrograms but may be significant below that level.

For neither the liver nor the plasma concentration of vitamin A was a correction made for the antimony trichloride color derived from the presence of carotene or carotenoids. The blue reaction due to vitamin A develops immediately and fades much faster than that due to carotene. Reliable information is not available as to how much of the immediate blue color is due to carotene. Our figures may, therefore, be influenced to a small degree by carotene.

<sup>22</sup> Baxter, J. C., and Robeson, G. D. *J. Am. Chem. Soc.* **64**: 2411, 1942.

<sup>23</sup> Skurnik, I., and Suhonen, P. *Ztschr. f. Vitaminforsch.* **8**: 316, 1939.

For histologic examination, the specimen of liver was fixed in solution of formaldehyde U S P diluted 1:10. After one hour frozen sections were examined under the fluorescence microscope for content and distribution of vitamin A.<sup>24</sup> Vitamin A gives a characteristic green fluorescence, which fades quickly owing to the irradiation. The specificity of this fluorescence has been established.<sup>24</sup> The exact localization of the fluorescence was examined in sections stained with methylene blue, which were studied both under ultraviolet rays and under visible light. The fat distribution was studied with an extremely sensitive fluorescent stain for fat, phosphor 3 R.<sup>25</sup> Fluorescence photomicrographs were taken of each specimen for permanent record.<sup>25</sup> In addition, frozen sections were stained with sudan III. The rest of the fixed specimen was embedded in paraffin and submitted to routine histologic examination.

#### FINDINGS AND ANALYSIS

*I Vitamin A Levels in Our Material*—Table 1 shows the plasma vitamin A levels determined before vitamin A was administered and before any operation. Because of the particular population of a charity hospital, these levels may not compare with those found in healthy persons or in patients of an economically better class. In addition, the hospital diet may cause variations. The values are presented to show the preliminary levels of the material on which further studies have been made. Owing to technical reasons the majority of our 167 subjects were male, and statistical conclusions are thus possible only for them. In patients with peptic ulcer or disease of the gallbladder without jaundice, in patients with miscellaneous diseases and in those admitted because of hernia or fractures, an average level of between 27 and 34 micrograms was found. In renal disease, in agreement with prior reports,<sup>26</sup> the average level was much higher. Confirming the observations of Abels and associates,<sup>27</sup> our results showed that patients with a malignant gastrointestinal neoplasm had a plasma vitamin A level about half as high as the level of the aforementioned groups. In patients recovering from an infectious disease<sup>28</sup> and especially in those with hepatic disease or obstructive jaundice, low, and often zero, levels were encountered, which is in agreement with the clinical vitamin A deficiency found occasionally in these conditions.

*Conclusion*—The variation encountered in the preliminary levels of vitamin A in the plasma of the 167 patients studied agrees with observations made by others. In this material the average plasma level lies around 30 micrograms per hundred cubic centimeters.

*II Change of Vitamin A Level During Operation (Possibly Due to Anesthesia)*—If the comparison between the vitamin A content of the plasma and of the liver is to be significant, the stability of the plasma vitamin A level must be examined during operation and anesthesia. Clausen and associates<sup>29</sup> have shown that after intake of alcohol the blood level of vitamin A rises owing to mobilization of vitamin A from the liver depots. On the other hand, the reduction of the prothrombin level (vitamin K) during anesthesia has been demonstrated.<sup>30</sup> Therefore, the

24 Popper, H., and Greenberg, R. Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, *Arch Path* **32** 11 (July) 1941.

25 Popper, H., and Elsasser, M. *Canad J M Technol* **3** 45, 1941.

26 (a) Hedberg, J., and Lindquist, T. *Acta med Scandnav* **90** 331, 1939. (b) Clausen, S. W., Baum, W. S., McCoord, A. B., Rydeen, J. O., and Breese, B. B. *J Nutrition* **24** 1, 1942.

27 Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, C. P. *J Clin Investigation* **20** 749, 1941.

28 Clausen, S. W., and McCoord, A. B. *J Pediat* **13** 635, 1938. Thiele, W. S., and Scherff, I. *Klin Wchnschr* **18** 1275, 1939.

29 Clausen, S. W., Breese, B. B., Baum, W. S., McCoord, A. B., and Rydeen, J. O. *Science* **93** 21, 1941. Clausen and others.<sup>26b</sup>

30 Allen, G. D., and Livingstone, H. *Anesthesiology* **1** 89, 1940.

influence of anesthesia and operation on the plasma vitamin A level was studied. Of 51 subjects, 35 had identical plasma levels before, during and after operation (fig 2B). In 16, a minor decrease of the level was noted (fig 2A), which, analogous to some observations on vitamin K, might be due to the anesthesia.

The following types of anesthesia were used: spinal (29 subjects), ether induced (13 subjects) and cyclopropane induced (9 subjects). However, no significant difference between the various types of anesthesia were noted. According to these observations, a fairly constant plasma level may be assumed, which confirms the observations of Stewart and Rouike.<sup>12</sup> In all comparisons with the liver content to be described later, the vitamin A level of the plasma during operation was used.

**Conclusion** The vitamin A level of the plasma does not appreciably change during operation.

**III Variation of the Vitamin A Content of the Liver**—The literature contains contradictory reports as to the variation of the content of vitamin A in different parts of the liver.<sup>31</sup> For 22 subjects we determined the vitamin A content from two different parts of the same biopsy specimen but found no significant difference.

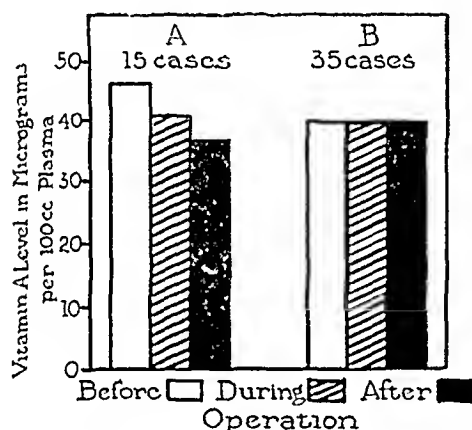


Fig 2—Averages of plasma vitamin A levels of 51 subjects before, during and after laparotomy. In 16 a slight decrease was found (A), in 35 no change was seen (B).

The maximum difference was 13 micrograms and the minimum 1 microgram with an average difference of 4 micrograms. This confirms our own experiences with animal livers.

Since surgical procedures during laparotomy might influence the vitamin A concentration of the liver,<sup>32</sup> two separate biopsies were made on 2 subjects, at the start and at the end of the operation. No appreciable difference was encountered (first biopsy 61 and 70 micrograms and second biopsy 58 and 66 micrograms per gram, respectively), in confirmation of the studies of Stewart and Rouike.<sup>12</sup> Under the fluorescence microscope, the first and second biopsy specimens checked also.

**Conclusion** No appreciable difference in the hepatic vitamin A concentration was found, in regard either to different parts or to the time of the biopsy.

**IV Comparison Between the Vitamin A Concentrations in the Plasma and in the Liver**—In our material the plasma vitamin A levels varied widely (fig 3). Low levels were encountered chiefly in patients with jaundice, high levels were

<sup>31</sup> Sen, K., and Sharma. *Indian J Vet Sc* 6:128, 1936. Rouike, G. M., and Stewart, J. D. *Composition of Liver*, *Arch Path* 33:603 (May) 1942. Lindqvist.<sup>14</sup>

<sup>32</sup> Young, G., and Wald, G. *Am J Physiol* 131:214, 1940.

found mostly in patients who received large doses of vitamin A. Both these facts enabled us to compare the liver content with a wide range of the vitamin A level in the plasma. If in a greater number of cases the average hepatic content is compared with the average plasma level, a parallelism between the vitamin A concentration in the liver and that in the plasma may be construed and is apparent in the statistical consideration of section V. If, however, the cases are considered individually, no direct parallelism existed between the vitamin A concentration in the liver and that in the plasma. Thus, a liver content of 110 micrograms per gram was at times found with a plasma level of only 7 micrograms and in another instance with one of nearly 70 micrograms per hundred cubic centimeters. At

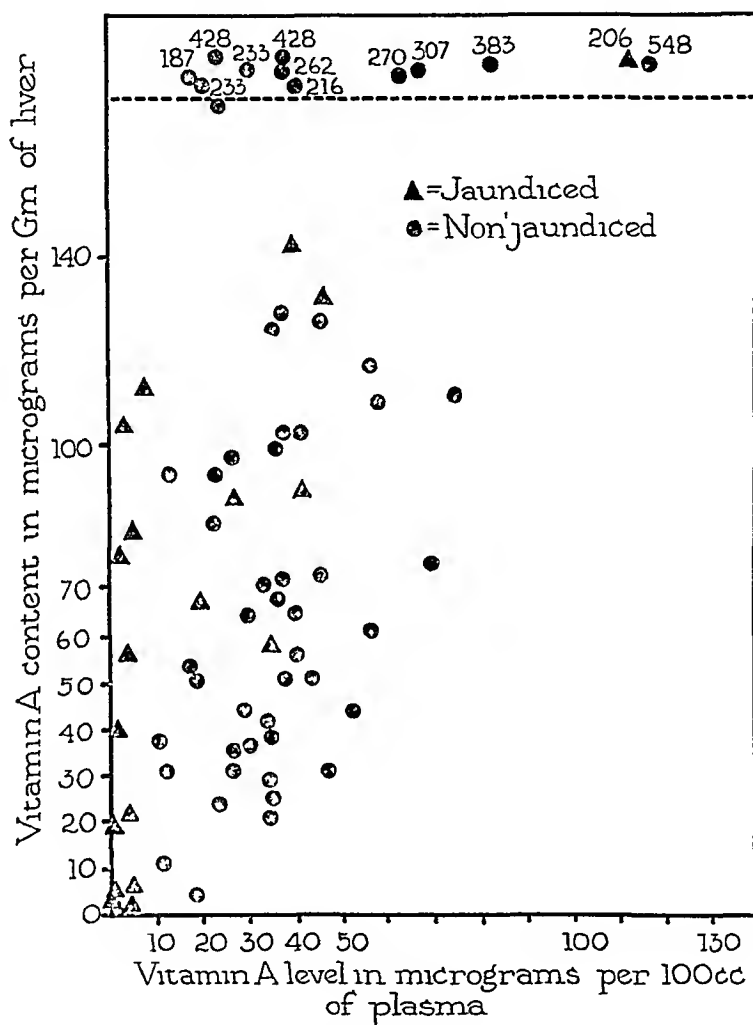


Fig 3—Vitamin A levels of the plasma during operation compared with the vitamin A content of biopsy specimens from the livers of patients with and patients without jaundice

other times a liver content of 56 micrograms per gram was encountered in a patient with a plasma level of 50 micrograms per hundred cubic centimeters. However, in all subjects with high plasma vitamin A level (over 60 micrograms per hundred cubic centimeters) the hepatic concentration was high. Low or zero values for plasma vitamin A were encountered with both relatively high and relatively low vitamin A content in the liver. The discrepancy between the concentration in the plasma and that in the liver was especially great in patients with jaundice. In these the plasma level was usually low despite a normal or only slightly decreased hepatic concentration of vitamin A.



**Conclusion** The vitamin A content in the plasma and that in the liver display a parallelism only when the plasma level is high

*V Comparison Between the Vitamin A Content of the Plasma and of the Liver and the Histologic Distribution of Vitamin A*—Comparison of Vitamin A Fluorescence and Vitamin A Content of the Liver In animal experiments under varied conditions, a parallelism between the vitamin A content (chemical) and the amount of vitamin A fluorescence was proved,<sup>33</sup> whereas in human subjects this parallelism seems questionable.<sup>34</sup> This study enabled us to compare the histologic and chemical methods as applied to the human liver

In table 2 the total amount of vitamin A fluorescence is indicated by symbols and compared with the chemical assay With few exceptions, the results of the two

TABLE 2—Comparison Between the Results of the Chemical Assay for Vitamin A and the Total Amount of Vitamin A Fluorescence in Biopsy Specimens of Human Liver, Arranged in Order of Chemical Vitamin A Content

Vitamin A Content, Micrograms/Gm of Liver	Estimated Total Amount Vitamin A Fluorescence	Vitamin A Content, Micrograms/Gm of Liver	Estimated Total Amount Vitamin A Fluorescence	Vitamin A Content, Micrograms/Gm of Liver	Estimated Total Amount Vitamin A Fluorescence	Vitamin A Content, Micrograms/Gm of Liver	Estimated Total Amount Vitamin A Fluorescence
0.2	± to —	37	+ to ++	70	+	121	+++
3.3	± to —	37	++	71	— to ++	122	+++
3.5	±	41	+	71	— +	124	+++
5	±	41	+ to ++	74	—	127	++ to +++
5.6	±	41	++	74	++	128	++
7	±	47	+	80	—	140	++
10	±	49	++	80	++	167	++
11	±	49	+++	86	++	187	++ to +++
19	++	50	+	88	+ to ++	206	++ +
20	+	52	+ to ++	91	++	216	+++ to ++++
22	+	55	+	92	—	222	++
24	+	55	++	96	++	222	++ to +++
25	++	56	++	97	++ to +++	262	+++
29	+	59	++	99	++ to +++	269	++
30	++	60	++	109	++	307	++
31	++	62	+ to ++	106	++	402	++
31	++	63	+ to ++	108	++	428	++
35	+ to ++	68	+ to ++	110	++	428	++
37	+	68	++	112	++	518	++
37	+						

methods check With some practice one is able from the histologic picture to predict the chemical result closely

Owing to this parallelism, the relation between the plasma vitamin A level and the total vitamin A fluorescence in the liver was found the same as between the plasma vitamin A level and the chemical assay

**Irregularity of Distribution of Vitamin A Fluorescence** In normal human liver (fig 4 A and B) vitamin A fluorescence is imparted by lipids in Kupfer cells and in the epithelial cells by fine lipid droplets at the edge of the cells, by a few medium-sized or large fat droplets, by lipofuscin, by mitochondria and by the cytoplasm Some of the these lipids may not be demonstrable by sudan III but

33 Popper, H, and Brenner, S J Nutrition **23** 431, 1942

34 Schairer, E, Rechenberger, J, Gockel, H, and Patzelt, K Virchows Arch f path Anat **305** 360, 1939

are visualized by staining with phosphor 3 R. The vitamin A distribution varies somewhat, even with identical total amounts of vitamin A and in livers which are normal on routine histologic examination<sup>8b</sup> (fig 4 C)

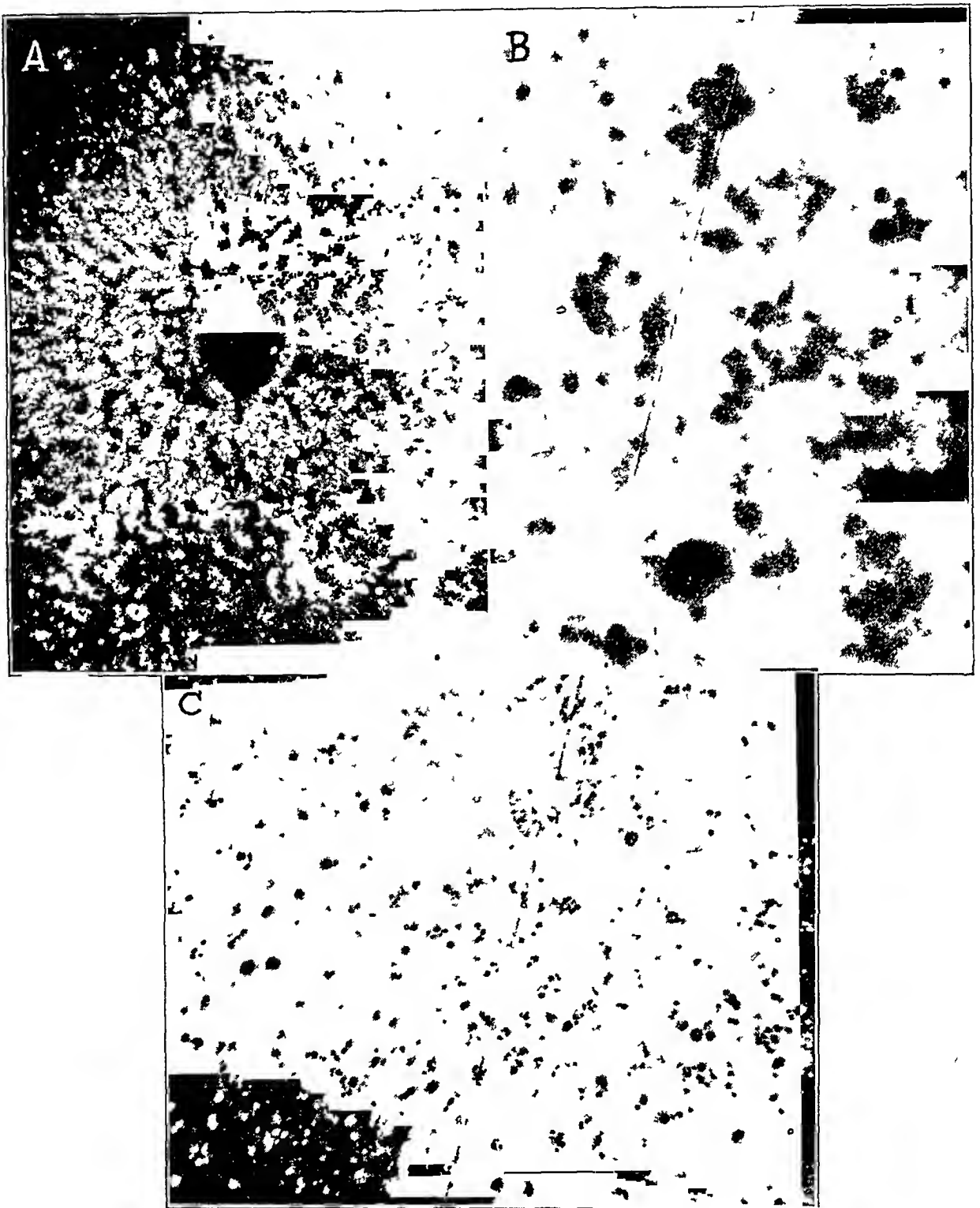


Fig 4—Fluorescence photomicrographs of biopsy specimens of liver *A*, normal distribution of the vitamin A fluorescence which is imparted by Kupffer cells, fine lipid droplets in liver cells and by a few irregularly scattered, large fat droplets, the diffuse dull fluorescence of the cytoplasm is not recognized in this photograph, *B*, high power field of a human liver with regular vitamin A fluorescence imparted by relatively large droplets in the Kupffer cells and by fine droplets at the edge of the liver cells, *C*, slightly irregular distribution of the vitamin A fluorescence in a liver without any signs of parenchymatous damage on routine histologic examination

Actually, no human liver examined showed the even and regular distribution of the vitamin A fluorescence found in experimental animals, which suggests that in patients coming to operation the structure of the liver is not completely normal. Practically all human livers examined by routine histologic methods showed some changes in the periportal fields, i. e. round cell infiltration. Pathologic changes of the parenchyma, however, are less easily recognized by routine examination. The deviations of the fluorescence microscopic picture from the normal are prevalence of vitamin A in Kupffer (fig 5 *A*) or liver cells (fig 5 *B*), development of medium-sized to large-sized fat droplets with high, low, absent or varying vitamin A fluorescence (fig 6 *A, B* and *C*), irregular distribution throughout the cytoplasm of the liver cells of small to medium-sized fluorescent fat droplets which normally are distributed only at the edge of the cells, bizarre shapes of the Kupffer cells outlined by the fluorescent lipid droplets in them (fig 7 *A*), great variation

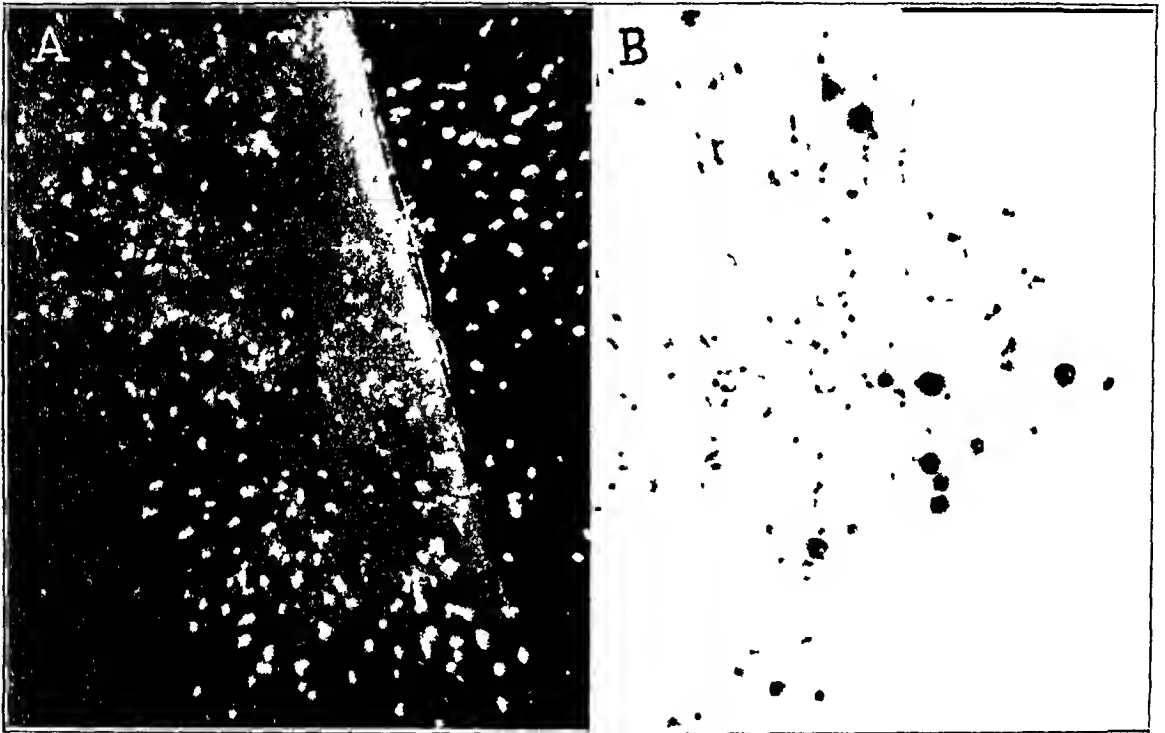


Fig 5—Fluorescence photomicrographs of biopsy specimens of liver. *A*, marked vitamin A fluorescence imparted almost exclusively by the Kupffer cells, *B*, marked vitamin A fluorescence almost exclusively imparted by fine droplets and a few irregularly scattered, large fat droplets in the liver cells.

in the morphologic details from cell to cell, often characterized by small foci with a fluorescent vitamin A pattern completely different from the other (fig 7 *B*). Not all of these variations are apparent in visible light. Some of the variations within the lobules are limited to certain areas of the lobule and are probably not pathologic but rather due to functional changes. Such variations are also found in healthy experimental animals under varied nutritional conditions<sup>35</sup>. Thus, the absence of vitamin fluorescence from the immediate central or peripheral areas is not necessarily pathologic. The diffuse vitamin A fluorescence of the cytoplasm varies greatly. If to these variations of the vitamin A fluorescence the appearance of other fluorescent details are added, such as brown-red lipofuscin fluorescence

35 Popper, H., and Steigmann, F. To be published.

green, not fading, bilirubin fluorescence, black spots due to lack of fluorescence of the bile casts and red hematoporphyrin fluorescence as seen in some cirrhotoses, an impressive variability of the fluorescence picture may result. In table 3 the degree of variability is compared with the incidence of pathologic changes on routine histologic examination associated with the average liver and plasma levels of vitamin A. In the subjects with marked variability, pathologic changes of the

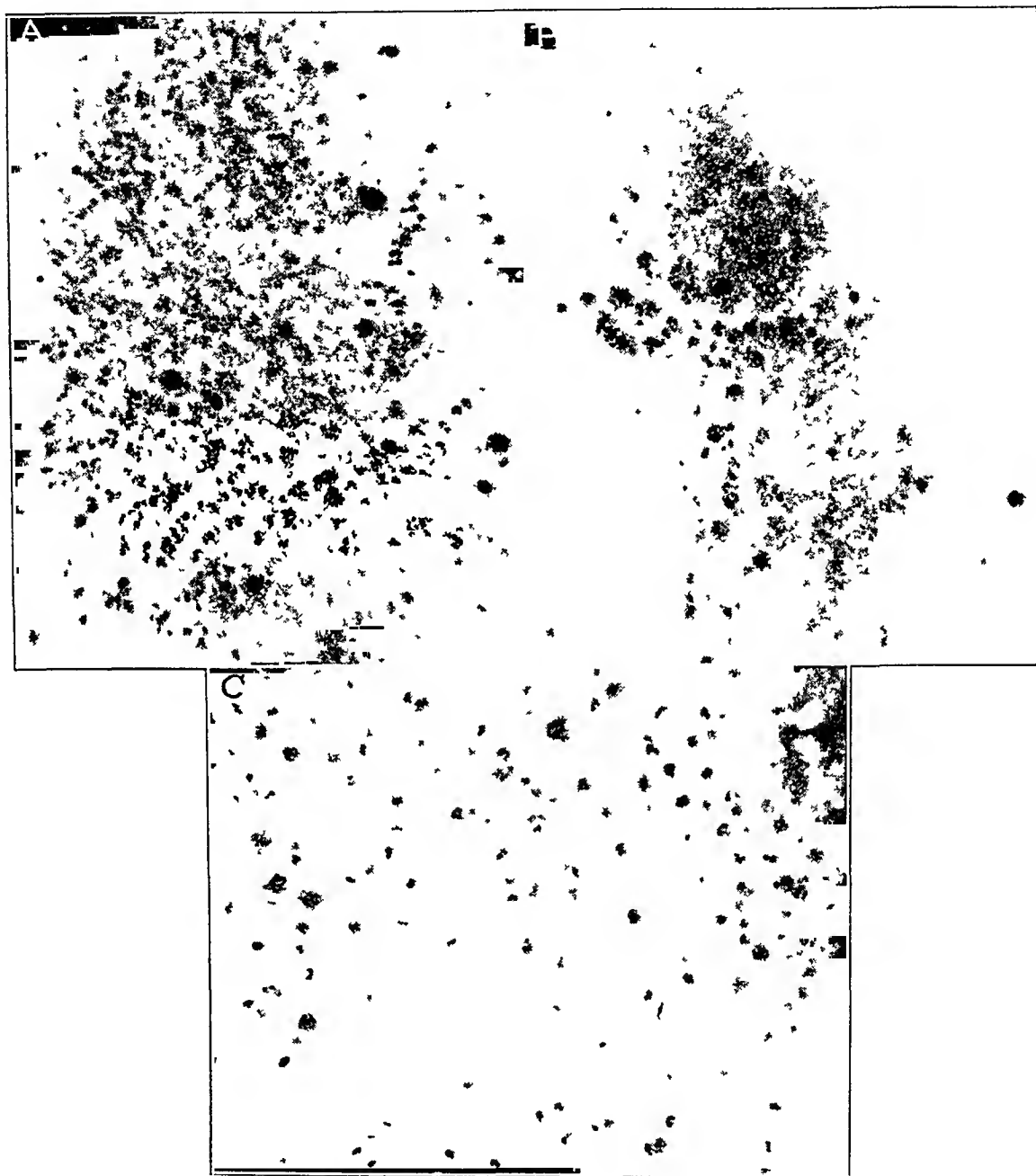


Fig 6—Fluorescence photomicrographs of biopsy specimens of liver *A*, marked vitamin A fluorescence of large, fat droplets, which is stronger than that of the Kupffer cells, in a liver which appears normal on routine histologic examination, *B*, variable vitamin A fluorescence in the large fat droplets in a cirrhotic liver (a few bizarre-shaped Kupffer cells impart vitamin A fluorescence), *C*, fat droplets showing nearly no vitamin A fluorescence as compared with the marked fluorescence of the Kupffer cells in a patient with disease of the gallbladder without jaundice

parenchyma, such as central and milary necroses and interstitial hepatitis, are encountered, the plasma and liver concentration of vitamin A shows a tendency to be low. The latter corresponds to the low vitamin A fluorescence usually

TABLE 3—*Relation Between Degree of Disturbance of Vitamin A Fluorescence Pattern and Pathologic Changes in the Liver and the Vitamin A Concentration in Liver and Plasma*

Degree of Disturbance of Vitamin A Fluorescence Pattern	Number of Subjects	Pathologic Changes in Liver		Average Concentration of Vitamin A	
		Number of Subjects	Percentage	Mg /Gm of Liver	Mg /100 Cc of Plasma
Plus minus	6	0	0	110	38
Plus	26	2	8	113	38
2 plus	24	3	12	104	31
3 plus	13	10	77	51	14.5
4 plus	7	7	100	27	7

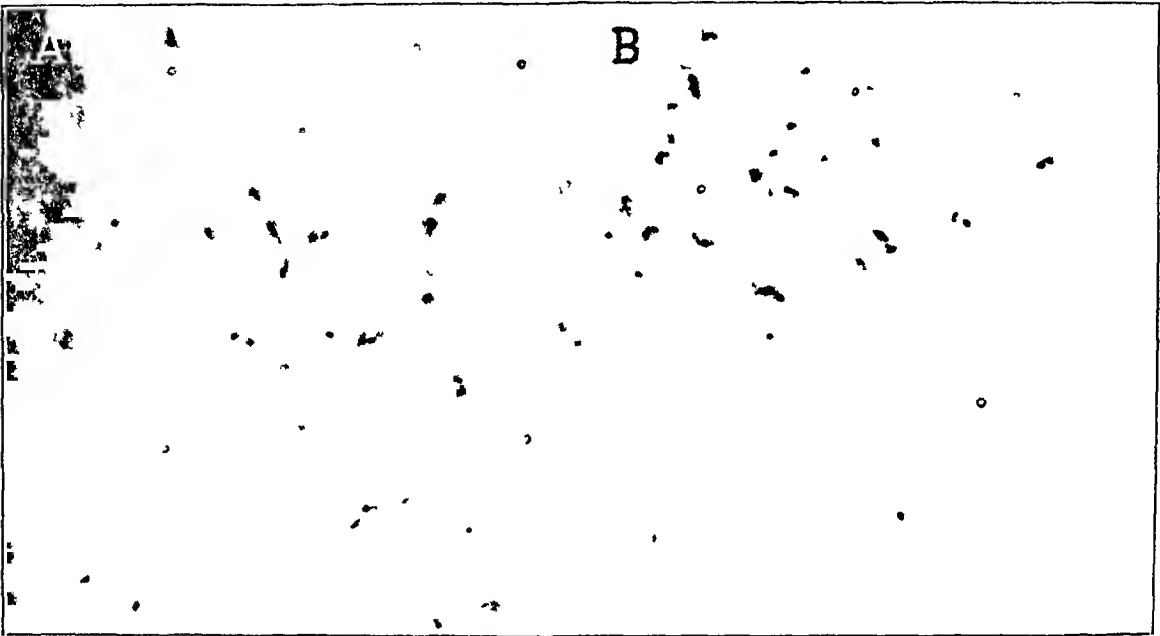


Fig 7—Fluorescence photomicrographs of biopsy specimens of liver *A*, vitamin A fluorescence imparted by a few bizarre-shaped Kupffer cells in a jaundiced patient with a malignant neoplasm of the biliary tract and low hepatic concentration of vitamin A, *B*, relatively marked vitamin A fluorescence imparted by Kupffer cells and fine droplets in the liver cells in a circumscribed area, whereas the surrounding areas are almost devoid of vitamin A fluorescence (there was no difference between the two areas on routine histologic examination)

TABLE 4—*Relation Between the Vitamin A Fluorescence in the Kupffer Cells and Liver Cells as Compared with the Pathologic Changes in the Liver and with the Vitamin A Concentration in Liver and Plasma*

	Degree of Prevalence of Vitamin A Fluorescence in Kupffer Cells Over That in Liver Cells			Vitamin A Equal in Kupffer Cells and Liver Cells	Degree of Prevalence of Vitamin A Fluorescence in Liver Cells Over That in Kupffer Cells		
	3 Plus	2 Plus	1 Plus		1 Plus	2 Plus	3 Plus
Number of subjects	5	13	21	23	8	5	1
Percentage with pathologic changes	20	15	19	44	50	20	0
Average vitamin A concentration in micrograms per gram of liver	177	147	133	69	51	43	41
Average vitamin A concentration in micrograms per 100 cc of plasma	53	35	35	25	20	20	27

observed in association with great variability of the histologic picture. At present the cause and significance of most of the variations is unknown. It may be suspected that the absence of vitamin A from the fat often encountered in cirrhosis may have something to do with choline deficiency<sup>36</sup>. Some variation may be caused by other nutritional alterations.

**Prevalence of Vitamin A Fluorescence in Kupffer Cells** The prevalence of vitamin A in Kupffer cells has been noted when the vitamin is fed in excess<sup>37</sup>. Generally when high amounts of vitamin A are found, the Kupffer cells are rich in

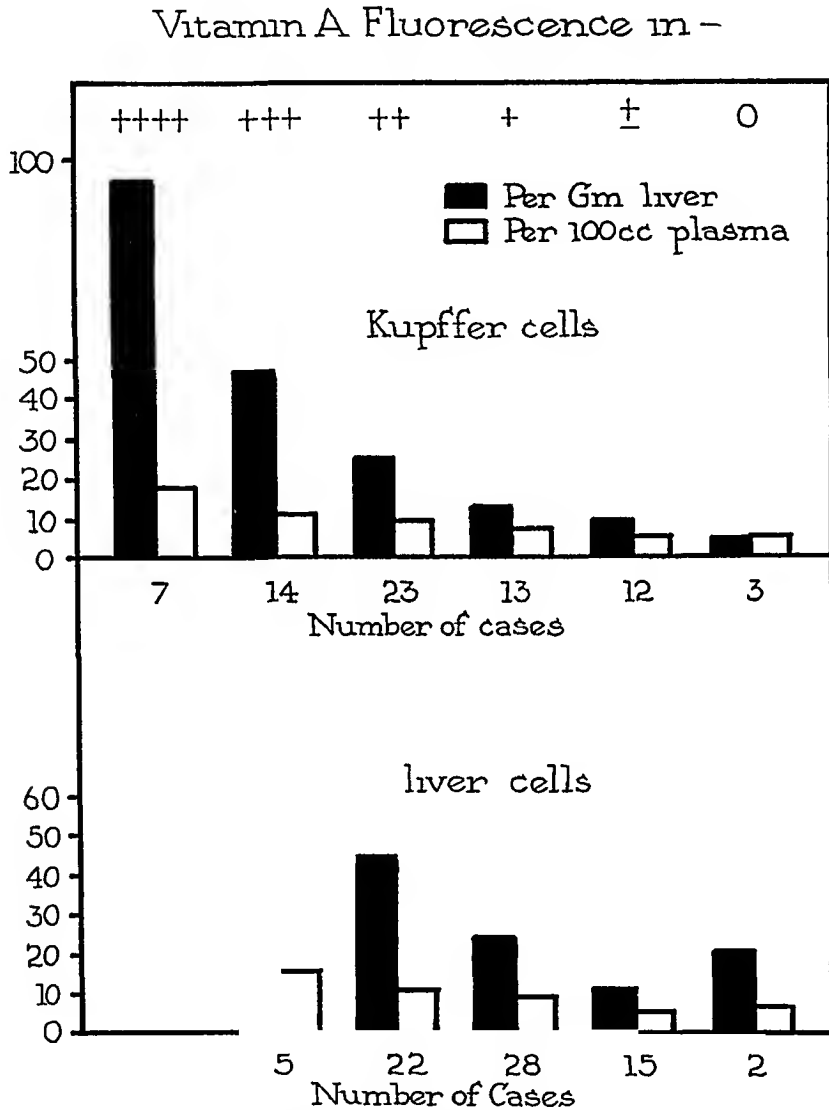


Fig 8—Comparison of the degree of the vitamin A fluorescence in Kupffer cells and in liver cells with the concentration of vitamin A in liver and plasma

it<sup>3b, c</sup>. This study provides an opportunity to compare the amount of vitamin A fluorescence in Kupffer cells and in liver cells with the concentrations in the plasma and the liver (fig 8). If average levels are compared, the amount of vitamin A fluorescence in Kupffer cells is in proportion to the total amount of vitamin A in the liver. The vitamin A fluorescence in the liver cells varies also proportionally but

<sup>36</sup> Popper, H, and Chinn, H. Proc Soc Exper Biol & Med **49** 202, 1942

<sup>37</sup> Hirt, A, and Wimmer, K. Klin Wchnschr **19** 123, 1940. Popper and Greenberg<sup>24</sup> Popper and Brenner<sup>33</sup>

to a lesser degree, shown by the fact that an extremely high (4 plus) vitamin A fluorescence in the liver cells was never found. The variation of the plasma level in comparison with vitamin A fluorescence in the Kupffer and liver cells is not marked.

The points emphasized are borne out by table 4, in which the observations are analyzed as to prevalence of vitamin A fluorescence in either Kupffer or liver cells. The higher the liver level the greater is the prevalence of the vitamin A fluorescence of the Kupffer cells over that of the liver cells, whereas the plasma levels are not as closely related. One may assume that, as in animals, excessive amounts of vitamin A in the liver are stored in the Kupffer cells. However, as in the experimental animals, not enough evidence is present to connect the high vitamin A fluorescence of the Kupffer cells with the vitamin A level in the plasma.

**Analysis of Results on Subjects with Discrepancy Between Plasma and Liver Vitamin A Concentration.** The fluorescence microscopic examination may be used to explain the discrepancy between plasma and liver vitamin A and also to aid in interpreting low or zero plasma levels. In this investigation we observed 6 instances of discrepancy between the vitamin A concentrations in the plasma and liver (table 5). The tests of hepatic function, when performed, showed severe impairment. The routine histologic examination revealed damage of the parenchyma. In all instances the distribution of vitamin A was highly irregular; there was, however, no specific disturbance of the pattern. The cytoplasm of the liver cells showed much green bilirubin fluorescence, and many black bile casts were seen. The fat droplets did not show vitamin A fluorescence, nor did most of the Kupffer cells. When Kupffer cells did show it, they were bizarre in shape and not adjacent to liver cells manifesting vitamin A fluorescence. When fine lipid droplets regularly lined the edges of the cells, they showed a rather irregular vitamin A fluorescence (fig 9A). All this suggests a disturbance in the normal relation between storage in Kupffer cells and that in liver cells. This, however, was not restricted to these subjects only and hence cannot be considered solely responsible for the discrepancy between the plasma and the liver concentration of vitamin A.

**Analysis of Results on Subjects with Plasma Vitamin A Level of Zero.** All 7 patients showed great variation of the vitamin A fluorescence pattern. In 1 of them the Kupffer cells only showed vitamin A fluorescence, in 2 of them nothing was seen in the Kupffer cells, while the remaining 4 showed vitamin A fluorescence in irregular distribution in both the Kupffer and the liver cells. The few scattered Kupffer cells imparting vitamin A fluorescence were bizarre in shape. In liver cells the fluorescence was found chiefly in medium-sized and large-sized fat droplets in an irregular distribution. In 3 subjects, many fat droplets without fluorescence were encountered, even fine lipid droplets at the edge of the cells failed to show vitamin A fluorescence. The characteristic feature in this group was irregular distribution and prevalence of fat without vitamin A fluorescence (fig 9B).

**Analysis of Results on Subjects with Plasma Vitamin A Level Below 7 Micrograms per Hundred Cubic Centimeters.** Six patients with a plasma vitamin A level above zero but below 7 micrograms revealed great variation in the vitamin A distribution. Most of them showed vitamin A fluorescence only in the intermediate zone, while in the central area there were usually biliary deposits and often biliary necrosis. The peripheral area revealed large cells with dark cytoplasm without vitamin A or fat. In most much brown fluorescent pigment of the nature of lipofuscin or iron was seen. Usually more vitamin A fluorescence was observed

TABLE 5—Laboratory Data in Cases of Marked Discrepancy Between Plasma Vitamin A Level and Hepatic Vitamin A Concentration

Sub ject	Diagnosis	Vitamin A Concentration		Degree Vitamin A Fluorescence		Observations on Routine Histologic Examination	Findings on Clinical Tests of Liver Function										Urinary	
		Micro- grams/ 100 Gm of Plasma	Liver	In Kupffer Cells	Total		Excretion of Hippuric Acid, Gm	Excretion of Alumen Gm	Phospha tase, Units	Cephalin Floccula tion Reaction	Albumin/ Globulin	Total Cholesterol/ Cholesterol Esters	Icterus Index	Takata Ara Reaction	Non protein Nitro gen	Uro bilino gen, Mg / 24 Hr		
P M	Obstructive jaundice with biliary cirrhosis	0	40	Not examined		Biliary cirrhosis with ex tensive recent necrotizing changes	3.6			—	1.6/3.8	200/131	150	++++	31			
J K	Cholangitis	0	50	+	+	Cholangitic and cholangio litic abscesses, toxic edema and Kupffer cell mobili zation in the surrounding liver tissue	1.0	0.6	40	++	3.1/2.2	305/241	37	0	54	26		
M R	Obstructive jaundice from carcinoma of pancreas	7	110	++	+	Central biliary necrosis, Kupffer cell mobilization in intermediary and peripheral zone, fibrosis of periportal fields with bile duct proliferation	1.0			—		394/198		—	34	1		
J N	Benign obstruc tion of the common duct with jaundice	4	80	++	±	Beginning interstitial hepa titis with intensive leukocytic infiltration	1.9			—			43	—	30			
E D	Obstructive jaundice from carcinoma of pancreas	6	55	+	±	Biliary necrosis surrounded by leukocytic infiltration, extensive fibrosis and leukocytic infiltration of the periportal field	1.11		12	++	2.9/2.5	147/42	75	0	12	9.68		
H B	Obstructive jaundice with biliary cirrhosis	0	74	+	+	Irregular size of liver cells, extensive central biliary necrosis, fibrosis and leukocytic and lympho cytic infiltration of the enlarged periportal field with regeneration of the surrounding parenchyma	2.5		58	—	3.3/3.1	200/33	100	+ +	31			



in the Kupffer cells than in the liver cells, the cytoplasm being free of vitamin A. The fine droplets occasionally observed at the edge of the cell were irregularly distributed and were usually not in the vicinity of Kupffer cells with vitamin A fluorescence.

**Conclusion.** Vitamin A fluorescence in the human liver parallels the hepatic concentration determined chemically. If high amounts of vitamin A are present in the liver, they are stored chiefly in the Kupffer cells. The normal pattern of distribution of the vitamin is altered if there is minor parenchymal damage; with severe damage the pattern presents greater changes than the alterations noted on routine histologic examination. These variations are marked in the case of

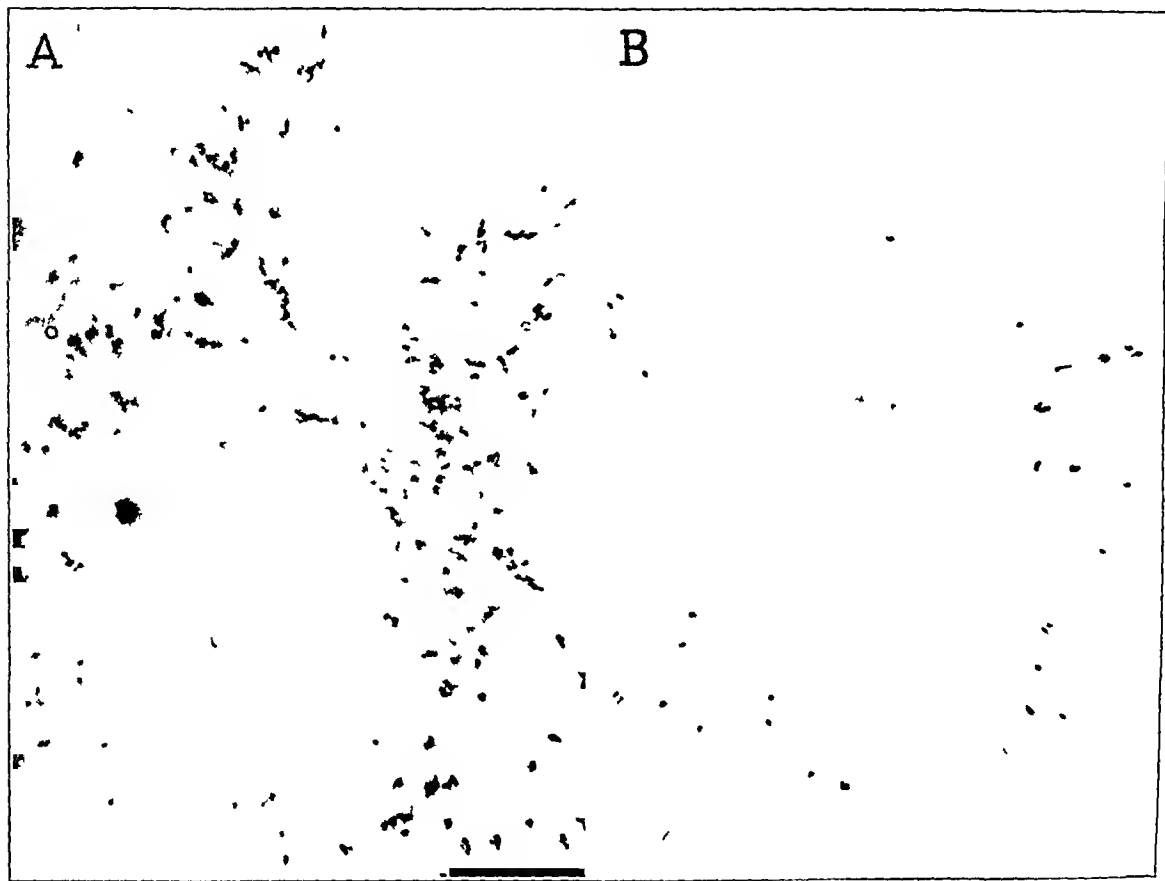


Fig 9—Fluorescence photomicrographs of biopsy specimens of liver. *A*, rather marked vitamin A fluorescence in extremely irregular distribution imparted by irregularly shaped Kupffer cells and by fat droplets of varying sizes and uneven distribution in the liver cells in a patient with obstructive jaundice and marked discrepancy between the hepatic concentration of vitamin A and the low plasma vitamin A level; *B*, slight vitamin A fluorescence imparted by a few Kupffer cells and isolated small fat droplets in liver cells in a patient with low vitamin A concentration in liver and plasma (malignant neoplasm of the biliary tract).

subjects with low blood levels of vitamin A, although pathognomonic morphologic changes could not be made out.

**Effect of Administration of Large Doses of Vitamin A.**—In all 7 subjects who received the huge supplements, of 500,000 U. S. P. units of vitamin A daily, the plasma level rose strikingly. Even zero levels, as in jaundice, and low levels, as in pyloric obstruction, reached at least normal levels (table 6). The vitamin A content of the liver was extremely high, even in the presence of hepatic damage. Although no preliminary hepatic levels were available the assump-

TABLE 6—Data on Patients Who Received Several Doses of 500,000 U S P Units of Vitamin A Before Operation

Name	Age	Sex	Diagnosis	Amount of Vitamin A Ingested, U S P Units		Vitamin A Level, Micrograms/100 Cc of Plasma		Amount of Carotene Level, Micrograms/100 Cc of Plasma		Carotene Level, Microgram per Gm of Liver	Vitamin A Fluorescence			Clinical Evidence of Hepatic Damage	Routine Histologic Evidence of Hepatic Damage			
				U S P Units	Preliminary	At Operation	Micrograms of Plasma	Vitamin A Level, Micrograms/100 Cc of Plasma	Carotene Level, Micrograms/100 Cc of Plasma		Total	In Kupfer Cells	In Liver Cells					
																Preliminary	At Operation	Total
I S	51	M	Carcinoma of stomach	2,650,000	10	44	123	50	56	13	+++	+++	0	0	Slight lymphocytic infiltration of periportal fields			
L O	28	M	Carcinoma of stomach	1,650,000	17	35	428	44	35	11	+++	+++	++	+	Slight lymphocytic infiltration of periportal fields			
G B	56	M	Carcinoma of stomach	3,075,000	44	109	548	147	147	27	+++	+++	+++	0	Fibrosis and lymphocytic infiltration of periportal fields			
T H	33	M	Tuberculosis of the stomach with pyloric obstruction	3,575,000	23	63	307	73	Trace	17	+++	+++	++	+	Kupffer cell mobilization with circumscribed small necroses			
M B	69	F	Cholelithiasis without jaundice	2,650,000	27	77	383	73	73	14	+++	+++	++	±	Irregular mitoses of liver cells, lymphocytic infiltration of periportal fields			
J D	62	M	Cholelithiasis with jaundice	2,650,000	44	105	205	47	50	43	+++	+++	+	+	Interstitial hepatitis, diffuse leukocytic and lymphocytic infiltration of parenchyma and periportal fields			
W Mc	60	M	Obstructive jaundice from carcinoma of ampulla of Vater	2,575,000	0	33	126	118	73	8	++	++	±	±	Central necroses, lymphocytic and leukocytic infiltration of enlarged periportal fields			

tion can be made that rather high amounts of vitamin A have been deposited in the liver. No increase of the carotene deposit, however, can be assumed.

The average amount of vitamin A in the liver of 5 nonjaundiced subjects receiving 500,000 U S P units of vitamin A daily was 366 micrograms per gram

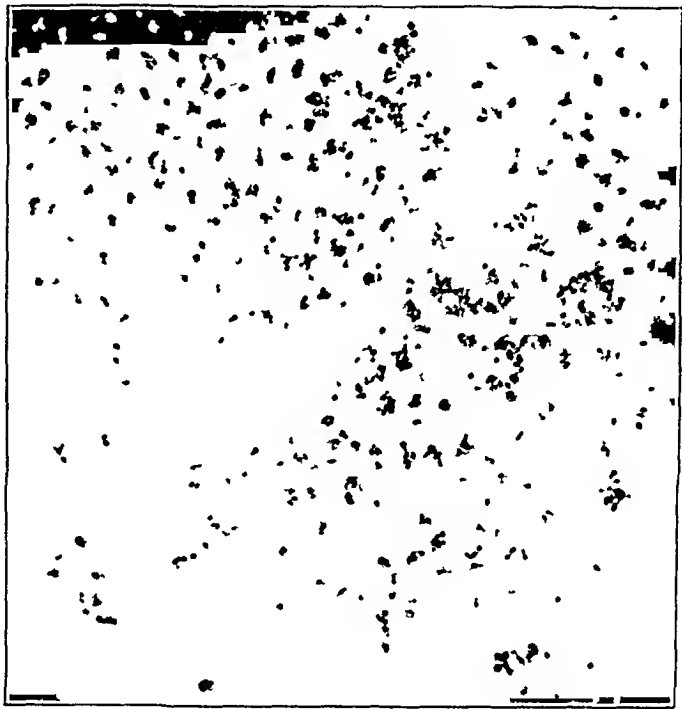


Fig 10—Fluorescence photomicrograph of a biopsy specimen of liver from a patient without hepatic damage after he had received six daily doses of 500,000 U S P units of vitamin A (pronounced vitamin A fluorescence imparted chiefly by the Kupffer cells and only to a smaller extent by fine lipid droplets at the edge of the liver cells)

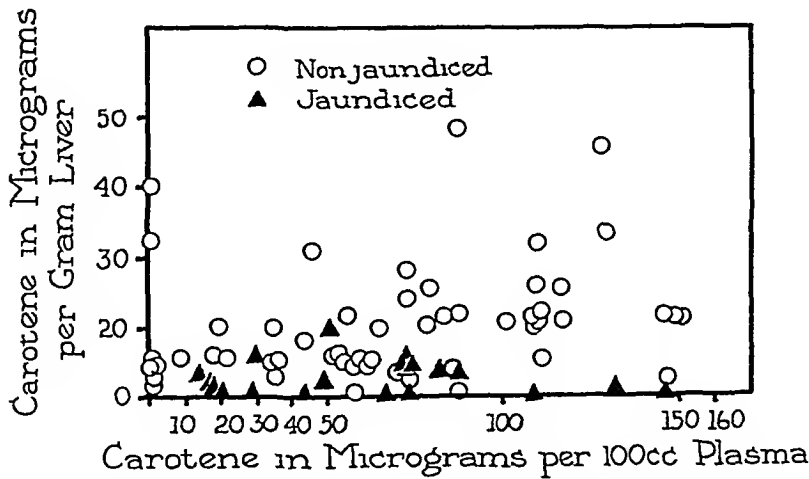


Fig 11—Carotene levels of the plasma during operation compared with the carotene content of biopsy specimens of liver from patients with and from patients without jaundice

If 100 micrograms is taken as the average hepatic concentration, an increase of 266 micrograms can be assumed. In a liver of 1,500 Gm the amount stored would be 390,000 micrograms or, with a conversion factor of 3.28, 1,279,200 U S P units of vitamin A. The patients received an average of 3,150,000 U S P

units each. Hence, one might presuppose that almost one half of the amount fed has been stored in the liver.

For 2 jaundiced subjects a similar comparison is impossible since an average of the hepatic concentrations of vitamin A could not be taken and the size of the liver was also unknown. If the latter is assumed to have weighed 1,500 Gm, it would mean that the average total amount was 811,800 U S P units. Since they each received 2,600,000 units of vitamin A, definitely much less had been stored in their livers than in normal livers, even if it is assumed that no vitamin A was previously present in the liver.

Also histologically by fluorescence microscopy extremely high amounts of vitamin A were encountered in the livers of all these patients. The vitamin A fluorescence was predominantly seen in the Kupffer cells (fig 10). In the 2 jaundiced subjects the vitamin A was seen not only in the pathologic areas, as in the fat droplets, but in the normal sites, in Kupffer and in liver cells.

**Conclusion** After administration of huge amounts of vitamin A, the vitamin A content of the human liver is increased strikingly even in jaundiced subjects, although to a somewhat lesser degree than in nonjaundiced subjects. The plasma level of the vitamin rises, but not to the same extent<sup>12</sup>.

*VII Studies on Carotene*—For all subjects studied, the level of carotene in the plasma and in the liver has been determined simultaneously with that of the vitamin A. A review of the carotene level in the specimens of plasma examined failed to show similar relations to diseases as the vitamin A level (table 1). During operation and during anesthesia no changes of the carotene level of the plasma were noted. Figure 11 shows that no definite relationship could be elicited between the carotene concentrations in the plasma and in the liver. The only noteworthy observation was that in jaundiced patients the level of carotene in the liver is usually low, which confirms the observations of Ralli and co-workers<sup>38</sup>.

**Conclusion** No characteristic behavior was indicated from the determinations of the carotene levels in plasma and in the liver.

#### COMMENT

The comparison between the vitamin A concentration in biopsy specimens of liver and the plasma shows that on the average subjects with a high hepatic concentration have a high plasma level and that subjects with a low plasma level have a low hepatic concentration. If, however, values for individual subjects are taken, no direct relation exists between the plasma level and the hepatic concentration of vitamin A. Similar results are found in the tables of Stewart and Rourke<sup>12</sup> and Abels and associates<sup>39</sup>. An attempt to use the plasma vitamin A level as an index of the vitamin A depots of the body of an individual subject is justified only if the plasma level is normal or, better still, if it is high, since a high plasma level points to a normal or high hepatic concentration. A low plasma level, on the other hand, does not necessarily indicate depleted liver stores. Since low plasma levels may coincide with normal or depleted liver depots, the question arises whether in subjects with normal liver depots and low plasma levels clinical vitamin A deficiency exists, in other words, whether the plasma level or the liver

38 Ralli, E. P., Popper, E., Paley, K., and Bauman, E. Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects, *Arch Int Med* 68:102 (July) 1941.

39 Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, A. B. *Proc Soc Exper Biol & Med* 48:488, 1941.

content indicates the vitamin A status of the body and thus the requirements for supplements of the vitamin

Primarily, one would be inclined to consider the liver level, which represents the vitamin A depots in the body, as an index of the vitamin A status. However, the results of fluorescence microscopic examination of the biopsy specimens of liver point rather to the plasma level as the indicator of the vitamin A status. The distribution of the vitamin A fluorescence varies greatly, which indicates that chemically identical amounts stored may have different functional significance. In animal experiments<sup>40</sup> we were able to show that in hepatic damage vitamin A shifts from normal sites, represented by Kupffer cells and by fine droplets at the edge of the liver cell, to pathologic sites, represented by large fat droplets. Furthermore if carbon tetrachloride-intoxicated rats are kept on a vitamin A-deficient diet, the vitamin A in the pathologic sites is less available for utilization. The vitamin A remains longer in the fatty than in the normal areas. In human material a disturbance of the distribution also occurs. Some degree of it was found in every specimen. It is more marked in pathologic livers although less uniformly than in the livers of the carbon tetrachloride-intoxicated animals. This disturbance of vitamin A distribution is especially pronounced in patients with jaundice. Thus, a shift of the vitamin A fluorescence from the Kupffer cells and fine droplets at the edge of the liver cells in human beings results in a very irregular and sometimes very bizarre picture, with a disturbance of the normal topographic relation between vitamin A fluorescence of Kupffer cells and liver cells.

All these changes indicate, in addition to the disturbance of the general hepatic function, severe disturbance of the vitamin A metabolism within the liver. Patients with discrepancy between plasma level (low) and liver stores (quantitatively normal) usually showed pathologic hepatic function on clinical examination and parenchymatous damage on routine histologic examination. All showed severe disturbances of the vitamin A distribution although a specific morphologic picture associated with such a discrepancy could not be ascertained. The disturbance in the distribution may explain the impaired release of vitamin A from the liver. Disturbances in the release of vitamin A were already suggested by several facts. In young rats the first signs of vitamin A deficiency appear after exhaustion of the liver depots,<sup>41</sup> whereas in older rats<sup>42</sup> and in other animals<sup>43</sup> traces of vitamin A may be found in the liver at such a time. In human subjects moreover, night blindness may appear while there is still considerable vitamin A in the liver. Thus, in diabetes mellitus<sup>44</sup> as well as in thyrotoxicosis<sup>45</sup> night blindness as a sign of vitamin A deficiency and even low blood levels<sup>46</sup> have been reported, in spite of the fact that the cadaver liver of a subject with this disease usually contains con-

40 Popper, H., Steigmann, F., and Dymewicz, H. A. *Proc Soc Exper Biol & Med* **50** 266, 1942

41 Dann, W. J. *Biochem J* **26** 1072, 1932. Baumann, Rising and Steenbock<sup>4b</sup>. Brenner, Brookes and Roberts<sup>10</sup>. Popper and Greenberg<sup>21</sup>

42 Davies, A. W., and Moore, T. *Biochem J* **31** 172, 1937

43 Guilbert, H. R., and Hart, G. H. *J Nutrition* **8** 25, 1934. Guilbert, H. R., and Hinshaw, R. *ibid* **8** 45, 1934. Leong, P. C. *Biochem J* **35** 806, 1941

44 Brazer, J. G., and Curtis, A. C. Vitamin A Deficiency in Diabetes Mellitus, *Arch Int Med* **65** 90 (Jan) 1940

45 Wohl, M. G., and Feldman, J. B. *Endocrinology* **24** 389, 1939. Zaffke, K. H. *Arch f Ophth* **140** 61, 1939

46 Wendt, H. *Munchen med Wchnschr* **82** 1660, 1935. Lindqvist<sup>1d</sup>

siderable amounts of vitamin A <sup>47</sup> Lindqvist <sup>2c</sup> found in pneumonia low serum levels of vitamin A but normal depots in the liver at necropsy

Many metabolites show an equilibrium in their balance between blood and liver. In the case of some metabolites, e. g. dextrose, <sup>48</sup> the blood level regulates the liver storage. In the case of vitamin A, on the other hand, at least under normal conditions the plasma level is obviously regulated and maintained by the liver. The liver is able to maintain for a certain length of time a normal blood level, even without nutritional supply <sup>49</sup>. In pathologic conditions this regulation by the liver is impaired, as seen from the data for subjects with a high hepatic concentration and a low plasma level. This disturbance of the release makes the plasma level more important for the recognition of vitamin A deficiency than the hepatic concentration, because only the circulating vitamin A is of functional value. Acute hepatic damage presents an example of this. The low plasma vitamin A level <sup>50</sup> and the night blindness <sup>51</sup> seen in catarrhal jaundice or in secondary hepatitis of obstructive jaundice <sup>12</sup> cannot be explained on the basis of disturbed intestinal absorption, since many months are required to deplete the healthy organism of vitamin A.

Clausen and associates <sup>26b</sup> have shown that in certain pathologic conditions (e. g. after ingestion of alcohol) an increased release of vitamin A from the liver into the blood may occur. An indication of such a process was not encountered in our material, although some histologic pictures may well be connected with such an occurrence.

#### SUMMARY

This study, performed by chemical methods and fluorescence microscopy, is concerned with the comparison between the plasma vitamin A level and the hepatic vitamin A concentration in human subjects under normal and under pathologic conditions.

The plasma vitamin A level showed great variations brought on by varied nutritional intake and by disease. It is moderately reduced in carcinoma of the gastrointestinal tract and greatly reduced in hepatic damage and in jaundice.

Anesthesia has little, if any, influence on the plasma vitamin A level. Comparison between the plasma level and the vitamin A concentration in biopsy specimens of liver over a wide range of the plasma vitamin A level (patients with jaundice, normal patients and patients receiving huge feedings of vitamin A) shows a parallelism between plasma and liver vitamin A concentrations only if the average of a fairly great number of cases is taken. If individual cases are considered no relation between these two factors exists. The plasma vitamin A level is thus no index of the liver stores of the vitamin, except that a high plasma level indicates normal or high stores. In contrast, low plasma levels may be associated with high or low liver contents of vitamin A.

The fluorescence microscopic picture shows great variations of the vitamin A fluorescence pattern. These variations are extremely marked in pathologic conditions of the liver and offer a possibility to recognize hepatic damage morphologi-

47 Moore <sup>13</sup> Popper <sup>8b</sup>

48 Soskin, S. *Physiol Rev* **21** 140, 1941

49 Murrill, W. A., Horton, P. B., Leiberman, E., and Newburgh, L. H. *J Clin Investigation* **20** 395, 1941. Steminger, Roberts and Brenner <sup>1c</sup>

50 Lasch, F. *Klin Wchnschr* **17** 1107, 1938. Breese, B. B., and McCoord, A. B. *J Pediat* **16** 139, 1940. Lindqvist <sup>1d</sup>

51 Wohl, M. G., and Feldman, J. B. *Am J Digest Dis* **8** 464, 1941

cally before it is revealed by routine histologic examination. The disturbance of the pattern is pronounced when there is great discrepancy between plasma and liver concentrations of vitamin A. Since apparently the plasma level is regulated by the liver, these pathologic changes in distribution of vitamin A explain disturbances in the release of the vitamin and the consequent discrepancy. In hepatic disease and in jaundice this disturbed release seems to be common. In general, the plasma level seems a better index for the functional status with regard to vitamin A than do the liver stores.

Intake of huge doses of vitamin A raises the concentration in the plasma and much more that in the liver. This increase is less pronounced in jaundice.

The amount of vitamin A fluorescence as seen under the microscope and the chemical assay for vitamin A (the method of which is discussed) run parallel in the human liver. If high amounts of vitamin A are present, they are chiefly found in Kupffer cells.

# CHANGES IN OPTIC FUNCTION AND OPHTHALMOSCOPIC PICTURE

OBSERVED IN FOUR PATIENTS OF THE EUNUCHOID SKELETAL  
TYPE WHO WERE BEING TREATED WITH  
AN ORCHIC EXTRACT

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In 1922 Stanley,<sup>1</sup> reporting on implantations of testicular substance, cited greatly strengthened vision in 32 of 41 inmates at San Quentin Prison who had previously complained of poor vision that necessitated glasses

My interest in orchic extract therapy was aroused by its use in the case of a man who presented the conditions of eunuchoidism and pituitary tumor with changes in the fundi and impairment of optic function After three months of therapy the ophthalmoscopic picture showed definite improvement This observation led to the use of this extract in the treatment of 3 other patients of the eunuchoid skeletal type, all of whom were found to have changes in the fundi and impairment of optic function The serial changes in the ophthalmoscopic picture were observed in the 4 patients so treated, for periods varying from seventeen months to two and one-half years The cases are reported for their suggestive value and to stimulate collaboration between the ophthalmologist, the internist and the endocrinologist confronted with patients showing similar findings The patients in cases 1 and 2 present eunuchoidism, while those in cases 3 and 4 present the eunuchoid skeletal disproportions but have normal sex development and function

## REPORT OF CASES

CASE 1—P B, a man aged 46, visited the medical clinic of the New York Polyclinic Medical School and Hospital Oct 31, 1938, where the diagnosis was made of pituitary tumor (chromophobe adenoma or craniopharyngioma) with the syndrome of diabetes insipidus, eunuchoidism, associated hypothyroidism, infection of the tonsils and possible dental infections He showed genital hypoplasia, a markedly infantile larynx with very short vocal cords There was no evidence of sinus disease (Dr W L Gatewood) The measurements were height, 64¼ inches (163 cm), span, 70¼ inches (178.5 cm), lower measurement, 37 inches (94 cm), upper measurement, 27¼ inches (69 cm) Roentgen examination (Dr Ernest E Smith) showed considerable enlargement of the pituitary fossa with destruction of the anterior and posterior clinoid processes on the left side and destruction of the floor of the sella, also a nonhomogeneous focus of calcification in the midportion of the fossa There was noncalcification of the epiphysial lines of the radius and the ulna The blood showed secondary anemia, and there was increased tolerance for sugar The Wassermann reaction of the blood was negative The basal metabolic rate was minus 23 Examinations of the sputum disclosed no tubercle bacilli

*Report on the Eyes*—The patient had previously visited Dr Erwin Torok's clinic in 1938 and again on Feb 8, 1939 for relief of blurred vision Glasses (convex sphere of 1.50 diopters for each eye) were prescribed for reading but without improvement On August 18 he still complained of impairment of vision, especially of that of the right eye Visual acuity then was 20/30 in both eyes The amplitude of accommodation was 2.75 diopters The right pupil was irregular and did not dilate after instillation of a solution of homatropine hydrobromide, especially at the outer and upper part Both pupils reacted promptly to light and accommodation The optic media were clear The optic disks were pale with blurred,

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From the Medical Clinic of the New York Polyclinic Medical School and Hospital  
1 Stanley, L L Endocrinology 6 793, 1922



indistinct margins, the right nerve head was pale, with large physiologic cupping, and the vessels were congested. The impression given was that of postneuritic optic atrophy, especially in the left eye. At this time the visual fields were almost normal for form but extremely contracted for red and green, with a central scotoma for these colors in each eye.

On September 29 (as reported by Dr. Joseph J. Fried, of Dr. Torok's clinic) the decoloration of the nerve heads was more marked. There was no definite blurring of the margin of the right disk, and the nasal half of the disk still showed definite congestion, the lamina cribrosa being very prominent. The left optic disk showed marked blurring along the nasal margin and at the lower half. The visual fields showed bitemporal contraction of about 25 degrees for form and extreme contraction for colors, a central scotoma for red and green was again noted. The color sense test (pseudoisochromatic plates) showed that the patient had difficulty in distinguishing certain shades of red and green. However, he promptly distinguished between red and green (5 and 10 mm test objects used in determining contraction of visual fields for form, 8 and 12 mm test objects used in determining contraction of fields for colors). The dark adaptation test (scotopicometer with Tscherning brightness no. 4) gave a result within the normal limits (fig. 2A).



Fig. 1 (case 1) —Roentgenogram of the sella turcica, left

*Additional History*—On November 28 he was admitted for eight days to the Polyclinic Hospital with cerebral concussion resulting from an automobile injury. At this time Dr. Abraham Kaplan, of the department of neurosurgery, reported on the appearance of the fundi as follows: "Bilateral optic atrophy, more on the right. No gross field defects."

*Therapy*—On July 13, 1939 hypodermic injections of a solution of an extract of orchic substance were begun. Each cubic centimeter of solution contained 114 mg. of a water-soluble heat-stable extract derived from 10 Gm. of fresh orchic substance. Glynn<sup>2</sup> has described the preparation of this extract as follows: An acid aqueous extract of bulls' testes is prepared and coagulated by heat to the point of boiling. The precipitate is removed, the filtrate, after concentration in vacuo, is taken up in 70 per cent alcohol, and the precipitate thus formed is filtered off. The 70 per cent alcohol-soluble fraction is evaporated in vacuo to remove the alcohol and precipitated with 4 volumes of acetone. The acetone precipitate is dried and taken up in water to such an extent that 114 mg. is contained in each cubic centimeter and represents the extract derived from 10 Gm. of fresh orchic substance. The solution is filtered until it is clear and sterilized by autoclaving. It is practically free from androgenic substance but contains significant amounts of inhibin. In common with all tissue extracts it contains

<sup>2</sup> Glynn, J. H. Personal communication to the author.

histamine in amounts that are not of therapeutic significance. There has been no assay for vitamin content. McCullagh<sup>3</sup> found that small quantities of this preparation (the orchic extract solution) will cause cessation of the estrous cycle in the normal female rat. He pointed out, however, that this does not necessarily indicate the presence of inhibin. Inhibin will cause cessation of estrous, but so will many other substances. The female rat test is therefore not specific for the hormone.

The first injection of 2 cc caused syncope and sweating. Subsequent injections were made with doses of from 1 to 2 cc twice weekly until Aug 14, 1941. Seven injections of testosterone propionate were substituted during the early part of these studies in order to determine a comparative response. Acetylsalicylic acid and brewers' yeast were given for grip and tonsillitis, which occurred during observation.

*Course*—On May 12, 1940 the patient reported improvement in eyesight, stating that he was able to read continuously for several hours, compared with a half hour three months before. Polyuria and polydipsia were much less. He felt subjectively better while under treatment. On Aug 14, 1941 the injections were discontinued for the purpose of having an examination of the eyes after the lapse of one month without them. On his return he

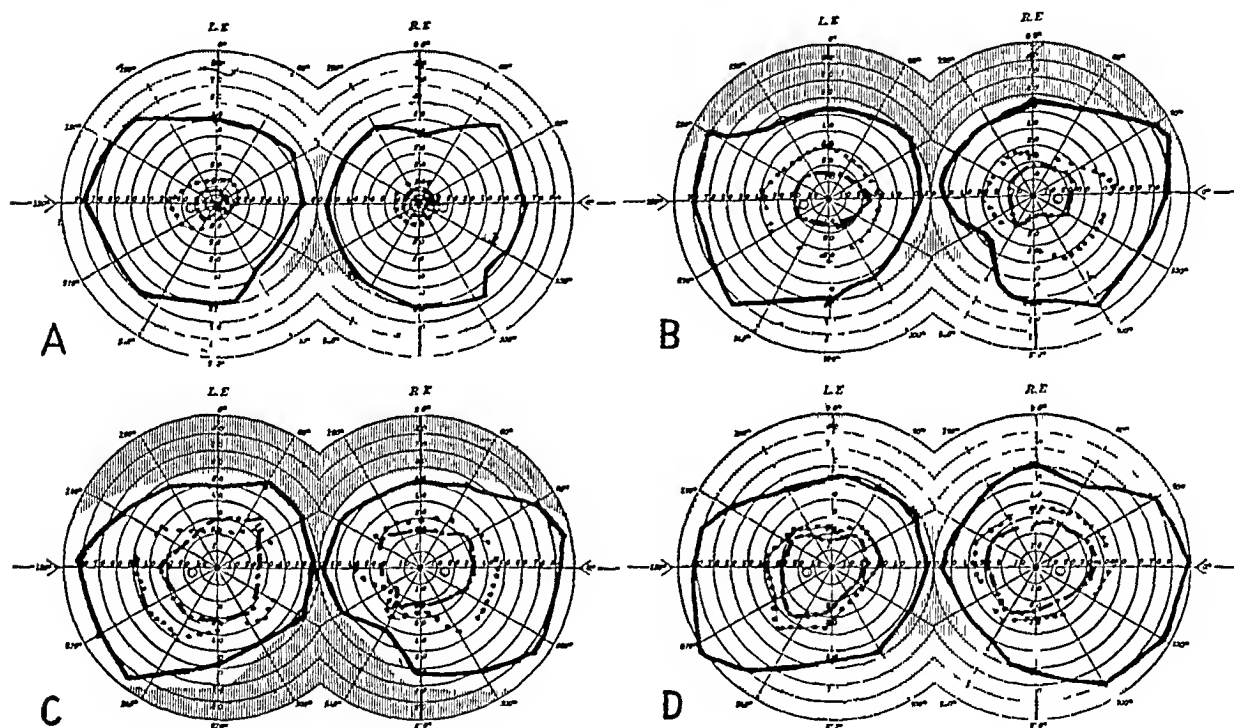


Fig 2 (case 1)—Charts of the visual fields. *A*, taken Oct 6, 1939, shows a central scotoma for red and green in each eye, *B*, taken May 11, 1940, *C*, taken Sept 24, 1940, *D*, taken Sept 12, 1941.

In these and all the subsequent charts the field limits as determined for form are indicated by a solid line, the field limits as determined for red, by a dotted line, the field limits as determined for green, by a dot-dash line. A central scotoma is indicated by a stippled area. The studies were made with an improved Forster perimeter, 5 mm test objects being used in determining the fields for form and 8 mm test objects (except when otherwise stated) in determining the fields for colors at a distance of 330 mm. The illumination used was that from a 75 watt Mazda lamp.

complained of having had weakness and soreness of the legs for three weeks. He was hospitalized at another institution shortly afterward.

*Subsequent Examinations of the Eyes* (Dr Joseph Fried)—Because of the presence of a pituitary tumor with the foregoing ophthalmic findings, frequent examinations were made of the visual acuity, accommodative power, fundi, visual fields and dark adaptation. On Dec 9, 1939 improvement was noted in the ophthalmic picture. The blurring of the disks had now disappeared, but marked bitemporal pallor of both nerve heads, especially of that in the left eye, was still present. The bitemporal crescentic defect for form had diminished,

3 McCullagh, D R. Personal communication to the author.

and the color fields had enlarged. No central scotoma was now noted in either eye. Visual acuity was 20/20 in both eyes. (On Aug 18, 1939 it had been 20/30 in each eye.)

On May 11, 1940 the visual acuity was 20/20 (20/15<sup>+</sup>) in both eyes (fig 2 B). The amplitude of accommodation had improved from 2.75 to 3.5 diopters. The pupils reacted promptly and dilated well. The fundi were well colored, the margins at the temporal and nasal parts of the disks were well defined and the retinal vessels were normal for the age. The visual fields showed further enlargement for colors as well as lessening of the bitemporal contraction for form.

On June 8, 1940, at a time when the patient had symptoms of grip, both fields showed regression for colors, being then similar to those found on March 6, 1940. By July 22 visual acuity was normal, and accommodative power had increased to 3.75 diopters, corresponding to age 44. The eyegrounds showed nothing abnormal. The visual fields, especially that in the left eye, again showed enlargement for colors as well as lessening of the bitemporal contraction for form.

On September 24 visual acuity was 20/20 (20/15<sup>+</sup>) in both eyes. There was further increase in accommodative power from 3.75 to 4 diopters (fig 2 C). The fundi were practically within normal limits. One could still trace the paleness of the temporal part of the right disk, the lamina cribrosa being decidedly less prominent. The left eyeground showed no pathologic change. The bitemporal contraction for form had practically disappeared, and for colors the fields were almost normal.

On Sept 12, 1941, after the omission of treatment for one month, visual acuity with correction was 20/20 in both eyes (fig 2 D), the amplitude of accommodation was 3 diopters (normal for the age), the pupils reacted normally, the fundi showed nothing abnormal except for beginning arteriosclerosis. The fields were normal except for slight contraction for red. Tests with the tangent screen and of dark adaptation and intraocular tension gave normal results.

On Oct 31, 1940 Dr Abraham Kaplan, who eleven months before, when the patient had cerebral concussion, reported the findings on examination of the fundi as "bilateral optic atrophy, more on the right, no gross field defects," now reported "Both disks are of good color except for some pallor on the temporal side of the right disk, there is no elevation of the disk, and the vessels are normal in color and caliber."

CASE 2—N. E., a man aged 53, single, had the characteristic features of eunuchoidism, the body was hairless, the penis was small, and the testes were not felt in the scrotum nor the prostate by rectal examination. The larynx was of the infantile type, with short vocal cords, there was no evidence of disease of the sinuses or the tonsils (Dr W. L. Gatewood). There were several infected teeth. The body measurements were height 71 $\frac{1}{4}$  inches (182 cm), span 73 inches (185.5 cm), upper measurement, 32 inches (76 cm), lower measurement, 39 $\frac{1}{4}$  inches (101 cm). The blood showed secondary anemia. The Wassermann reaction of the blood was negative. The urine was normal. The basal metabolic rate was minus 12. A roentgenogram showed the sella turcica to be of normal size and shape. On Oct 6, 1939 the visual fields revealed concentric contraction for form and color. The contraction for form was more marked temporally, especially in the left eye. Diminished visual acuity in the left eye coincided with the field findings. Visual acuity in the right eye was 20/100, with correction 20/20. In the left eye it was 20/70, with correction 20/40. The pupils were very small and oval horizontally.

*Examination of the Eyes* (Dr Joseph Fried).—On Dec 27, 1939 visual acuity was 20/200 in both eyes. A 1.75 convex sphere with a 0.25 convex cylindric lens, axis 180, improved vision to 20/20 in each eye. The amplitude of accommodation was 1 diopter, corresponding to age 60. The addition of convex 3.0 diopter lenses to distance glasses was required for reading of small type (Jaeger 1). The pupils were narrow (2.5 mm) and reacted promptly to light and accommodation. The retinas appeared pale, the larger retinal vessels were abundant, but the capillaries were very scant. There was marked decoloration of the temporal part of the left disk, with less marked temporal decoloration of the right disk. In the right eye there was enlargement of the physiologic excavation toward the temporal side of the nerve head. The visual fields showed concentric contraction for form and colors (fig 3 A), very markedly temporally. The tangent screen showed no enlargement of the blindspot or any kind of scotoma. The color sense was good, dark adaptation showed nothing abnormal, and there was no increase of intraocular tension.

*Therapy*.—Injections of the orchic extract were given at the rate of two a week from Oct 10, 1939 until Dec 18, 1941, after which they were omitted for seven weeks for a comparative examination of the eyes. During the early period of treatment a substitution of six injections of testosterone propionate in doses varying from 12.5 to 5 mg. was made in order

to note any comparative effect, and several weeks later three injections of chorionic gonadotropin in doses of 100 rat units each were given for the same reason. Brewers' yeast and cod liver oil were ordered for grip and bronchitis when these occurred. After March 19, 1942 several infected dental roots were extracted.

*Subsequent Examinations of the Eyes*—On Jan 15, 1940 definite temporal pallor of each disk was noted. The visual fields showed the same concentric contraction for form and colors, very marked temporally. The tangent screen showed no abnormal changes. The patient had good color sense (Holmgren test). Tests of dark adaptation (scotopicometer Moller) and intraocular tension gave normal results. After March 22 examinations revealed gradual disappearance of the bitemporal pallor of the nerve heads. The papillae became well colored and well defined, and the fundi showed no vascular changes other than those usually found at the age of this patient. The abundance of the capillaries now present was in contrast to their scantiness on Dec 21, 1939. On March 23, 1940 improvement in the fields was first noted. Thereafter gradual enlargement for white, red and green was recorded. By May 4 visual acuity had improved. Vision then without glasses was 20/100 in both eyes, compared with 20/200 previously, both eyes showed 20/20 with correction. The accommodative power showed considerable improvement. The amplitude of accommodation was 2.5 diopters (compared with 1 diopter on Dec 22, 1939), and correspondingly weaker lenses were required for near vision. The paleness of the fundi had disappeared, the retinas now having normal coloring. The visual fields were practically normal for form and were almost normal for colors.

On June 8 regression in the fields was noted. At this time the patient was recovering from grip. This proved temporary, for on July 22 the fields again showed improvement for form and colors.

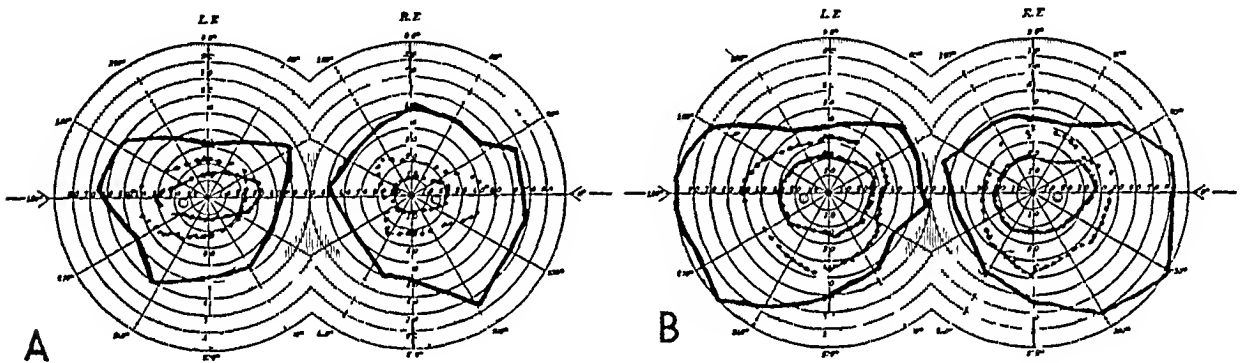


Fig 3 (case 2) —Charts of the visual fields. *A*, taken Dec 27, 1939, *B*, taken Sept 24, 1940. For further explanation of the charts, see the legend for figure 2.

By September 24 the outlines and the color of the disks were quite normal. No abnormal changes were seen in the fundi, the abundance of capillaries were still present. There was normal reaction to light and accommodation. The visual fields (fig 3 *B*) showed continued improvement, and the outlines at this time almost corresponded with those of May 4. Visual acuity was 20/100 in both eyes and 20/20 with correction. The improvement in the amplitude of accommodation noted on May 4 was still maintained.

On Jan 3, 1941, visual acuity in the right eye was 20/100, the addition of 2.5 diopters corrected vision to 20/20. The accommodative power was 2.5 diopters. The addition of +2.25 diopter spheric lenses in both eyes enabled him to read the smallest print (Jaeger's test type 1) at 10 inches (25 cm). The pupils were very narrow (1.5 to 2.0 mm), and the reaction to light and accommodation was difficult to determine. Under dilatation, the retinas and the choroids appeared normal, the nerve heads were well colored and well outlined, the arteries were undulated, with thickened walls, and the capillaries were abundant. The fields were normal for form and colors. Dark adaptation, the tangent screen, color sense (pseudo-isochromatic plates) and intraocular tension showed no abnormalities.

On Feb 6, 1942, after omission of treatment since Dec 18, 1941, examination revealed normal function of the eyes and no signs of pathologic change of the eyegrounds, visual fields or refraction. The amplitude of accommodation continued improved so that weaker lenses (between 1.75 and 2 diopters) were required for reading. The chart of the visual fields corresponded to that of Sept 24, 1940.

**CASE 3**—H J, aged 60, a widower, attended the medical clinic Oct 17, 1940. He presented eunuchoid skeletal measurements and female distribution of pubic hair but normal sex development and function. He had tertiary syphilis, cerebral arteriosclerosis, with the residuum of a

recent focal lesion in the left temporal lobe which caused impairment of speech, and probably dental infection. The measurements were height,  $65\frac{7}{8}$  inches (167 cm), span, 70 inches (178 cm), lower measurement, 34 inches (86 cm), upper measurement,  $31\frac{7}{8}$  inches (91 cm), nude weight,  $122\frac{3}{4}$  pounds (55.5 Kg). Roentgenograms were negative for sinus disease, and the sella turcica appeared normal. The blood count and the urinalysis gave normal results. The figures for blood sugar, uric acid and cholesterol were normal. The Wassermann reaction of the blood was negative with alcohol antigen and 2 plus with cholesterol antigen, the Kahn reaction was 3 plus. The patient would not permit examination of the spinal fluid. The basal metabolic rate was minus 4.

*Report on the Eyes* (Dr Joseph Fried)—On Oct 18, 1940 visual acuity was 20/30 in the right eye and 20/40 (?) in the left eye. As to near vision, he was able to read Jaeger's test type 3 with the right eye and Jaeger's test type 5 with the left. Vision could not be improved by adding lenses. The amplitude of accommodation was 0.25 diopter, corresponding to an age of about 65 years. Motor function of the eyeballs was fairly good, and the optic media were clear. Both eyegrounds showed pale, decolorized, whitish gray optic disks with ill defined and blurred margins, especially the left eyeground temporally. There was no pathologic change in the choroid, the retina or the retinal vessels in either eye. The visual fields showed concentric

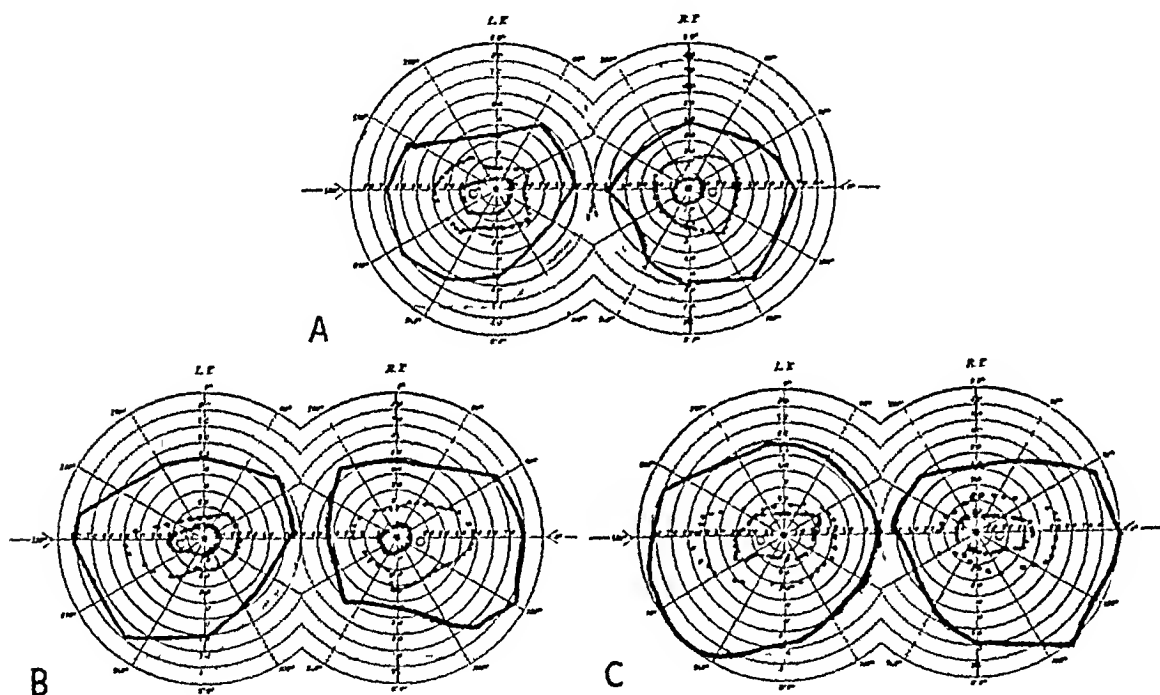


Fig 4 (case 3)—Charts of the visual fields. *A*, taken Oct 23, 1940 (10 mm test object used in determining fields for colors), *B*, taken March 15, 1941, *C*, taken Oct 6, 1941 and Feb 5, 1942 (10 mm test object used in determining fields for colors). For further explanation of the charts, see the legend for figure 2.

contraction for form and color (fig 4*A*), and there was decreased dark adaptation (six minutes with Moller's scotopicometer). At this time a diagnosis of bilateral optic atrophy was made, but there was doubt as to whether this was due to arteriosclerosis, syphilis or post-neuritic atrophy of the optic nerve.

*Therapy*—The patient had received antisyphilitic treatment for two and one-half years. On Nov 11, 1940, two months after antisyphilitic treatment had been suspended, injections of orchic extract were begun. Doses varying from 2 to 0.5 cc were given twice weekly until Feb 16, 1942. The treatment was then discontinued in order that the eyes might be examined after two months' omission of treatment. On January 6 he was referred to the dermatology clinic (Dr Jerome Kingsbury), where weekly injections of a bismuth preparation were started.

*Course*—The patient felt stronger during the treatment with orchic extract. Three months after treatment with the extract had started, at a time when he had a cold, a change appeared at the temporal side of the left eye suggesting bluish smoke with occasional threads like soot in front of it. This has occurred about six times during the past five years. When it recurred

on March 10, 1941 he was referred to the ophthalmology clinic (See examination of the eyes of March 15, 1941) On June 24 he had the first of several dental extractions, but he still retains a gold-capped tooth

*Subsequent Examination of the Eyes* (Dr Joseph J Fried) —On Nov 27, 1940 decoloration of both optic nerves was still present Visual acuity was 20/30 in the right eye and 20/40—2 in the left eye, there was some enlargement for green in the visual fields as compared with the finding on Oct 18, 1940

On December 30 vision was 20/20—2 in the right eye and 20/25—2 in the left eye, and 20/25 with correction, the near point was 530 mm for each eye, the right pupil measured 6 mm, the left, 7 mm, the right pupil was irregular, and there was poor response to light and accommodation The fields were almost normal for form, there was still concentric contraction for red and green The disks were now well colored and well outlined

On Feb 28, 1941 visual acuity was improved The right eye was 20/20, the left eye was 20/25 Near vision (reading of Jaeger's 1 test type) was obtained with +3.5 diopters for both eyes The pupils were the same size as on Dec 30, 1940, and both reacted fairly well The nerve heads now appeared well colored and well outlined, there was a peripapillary choroidal atrophy at the temporal margin of the left disk The retina, the choroid and the retinal vessels in each eye were normal The dark adaptation was normal at this time (three minutes) The visual fields showed improvement for form but not for colors There was a striking change in the appearance of the fundi as compared with their appearance on Oct 18, 1940

On March 15, 1941, five days after the recurrence of the bluish smoke in the temporal part of the left eye, the left disk appeared paler than at the previous examination, the temporal margins of the disks were ill defined and there was peripapillary edema of the retina (fig 4 B) Vision in the right eye was 20/30, vision in the left eye, 20/50, improved with glasses to 20/25 One week later the peripapillary retinal edema and blurring of the temporal margins had disappeared, and visual acuity in the left eye was 20/30 without correction

On October 6 the first positive enlargement of the visual fields for color was noted Visual acuity was 20/20 in each eye with correction The amplitude of accommodation corresponded to the age of the patient Near vision (reading of Jaeger's test type 1) was obtained with +3.5 diopters in both eyes The optic disks were well colored and well defined No pathologic change was seen in the retina, and there were no signs of arteriosclerosis The arterioles were distinctly seen There were no corkscrew maculopapillary venules The dark adaptation was normal The visual fields were normal for form, their contraction for colors was diminished (fig 4 C)

On Feb 5, 1942 vision in each eye was 20/20 with correction and reading of Jaeger's test type 1 (near reading) was obtained with +3.5 diopters The eyegrounds were normal The visual fields were almost normal for form (fig 4 C) For colors, though improved, they were still narrower than normal The findings on April 16 corresponded to those of February 5 He had received no injections of orchic extract between these dates Injections of a bismuth preparation were begun on Jan 6, 1942

CASE 4—R E, aged 42, married, an attorney, during a regular visit with his son, a pituitary dwarf, became emotionally upset while relating his financial reverses His depressed spirits prompted the injection of orchic extract A week later casual questioning elicited the unexpected report that he had noticed perceptible clearing of the head and decided clearing of vision, especially for street lights, while driving home after the injection the week before The same evening he was able to read printed matter without glasses He had never experienced this before He was also relieved of a quite constant pressure over the eyes and lower part of the forehead which had troubled him for several years On this information he was referred for an examination of the eyes (See report for Dec 11, 1940) His parents are related as cousins Several brothers are over 6 feet (183 cm) tall He had the typical eunuchoid skeletal measurements and female distribution of the pubic hair but normal sex development and function The measurements were height, 71½ inches (182 cm), span, 74 inches (188 cm), lower measurement, 38 inches (96.5 cm), upper measurement, 33½ inches (85.5 cm), nude weight, 173¼ pounds (78.6 Kg) The heart was slightly enlarged to the left, the sounds were normal Roentgenograms showed the sella turcica larger than average but otherwise normal There was no evidence of sinusitis The frontal sinuses were considerably larger than average, and pneumatization of the ethmoid cells was more pronounced The blood count and the differential percentages were normal The blood sugar amounted to 105 mg, uric acid to 4 mg and cholesterol to 160 mg per hundred cubic centimeters The urine had a faint trace of albumin and a specific gravity of 1.032 but was otherwise normal The Wassermann reaction of the blood was negative The basal metabolic rate was minus 5

*Report on the Eyes* (Dr Joseph J Fried)—On Dec 11, 1940 examination showed wide palpebral fissures (12 mm) The oculomotor apparatus was intact Arcus senilis was present in both eyes There was prompt pupillary response Both disks showed slight pallor, the right more than the left, the arteries were markedly narrowed, with signs of premature sclerosis Hypermetropic astigmatism was present Visual acuity was 20/40 in both eyes without correction and 20/20 with correction The amplitude of accommodation was 2 diopters, corresponding to the age of 54 years The visual fields were normal for form and slightly contracted for colors, there were central scotomas for red (fig 5 A) The tangent screen showed a 7 degree downward enlargement of the blindspots

*Therapy*—The patient was given six injections between Dec 3 and 31, 1940, when the eyes were reexamined A total of twenty injections was given in the seventeen months that followed

*Course*—Two weeks after treatment had started he could read without the glasses which had been required for several years Vision in daylight had improved considerably He felt more alert Further injections gave complete relief from the feeling of pressure and fulness between the eyes and in the frontal region After February 1941 he had had several attacks of grip and received treatment at infrequent intervals His consumption of tobacco was unchanged

*Subsequent Examinations of the Eyes* (Dr Joseph Fried)—On Dec 31, 1940 visual acuity for distance was unchanged but there was improvement in near vision He read medium-sized newspaper print (Jaeger test type 3) without glasses At the first examination (December 11) he required the addition of convex 2.5 diopter lenses to read Jaeger's test type 1 at a dis-

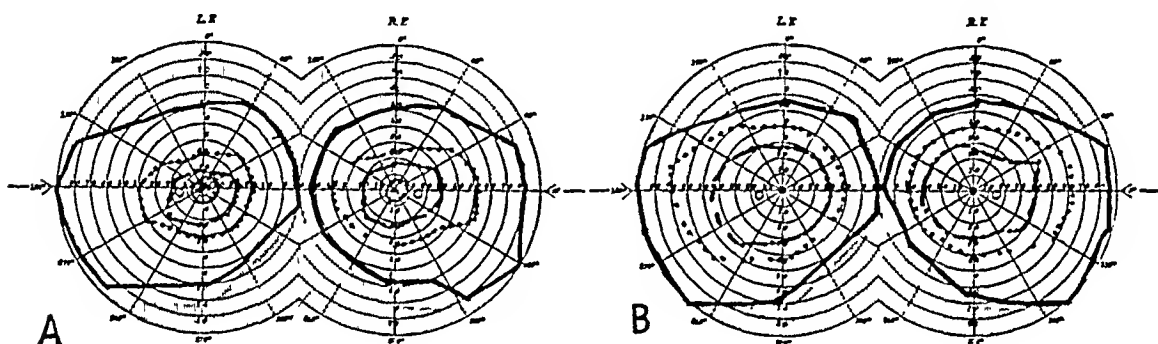


Fig 5 (case 4)—Charts of the visual fields A taken Dec 11, 1940, B, taken Oct 23, 1941 For further explanation of the charts, see the legend for figure 2

tance of 200 mm At the later examination the addition of convex 1.75 diopter lenses to distance-correcting lenses enabled him to read Jaeger's test type 1 The amplitude of accommodation had improved from 2 to 2.5 diopters The paleness of the right disk previously observed was not present The enlargement of the blindspot in the right eye diminished to the normal limits

On Feb 18, 1941 the same glasses were suitable for distance that were suitable on Dec 11, 1940 He read without lenses newspaper print at 540 mm distance with the right eye and at 410 mm distance with the left Using street glasses, he read the smallest print of the test chart for near reading at 400 mm with each eye The addition of convex 1.5 diopter lenses to the distance lenses enabled him to read the smallest print at 200 mm The amplitude of accommodation (2.75 diopters) corresponded to the age of 47 to 49 years There was normal oculomotor balance for distance and near There was a return of the slight pallor of the right nerve head, present at the initial examination on Dec 11, 1940 but absent on Dec 31, 1940 The visual fields and tangent screen tests did not show the central scotoma for color and the enlarged blindspots noted at the first examination The amplitude of accommodation was the same as on Dec 31, 1940 (The patient was recovering from grip at the time of this examination)

On Oct 23, 1941 the palpebral fissures were of normal width (10 mm) The optic disks were well colored and well defined, and the retina and the choroid were of normal appearance However, the arteries were narrower than normal The visual fields and the findings with the tangent screen were normal (fig 5 B) There were no central scotomas for color or enlargement of the blindspots The visual acuity showed decided improvement Distance vision without glasses was 20/20 in both eyes, and the amplitude of accommodation was 4.5 diopters, corresponding to age 40, so that the reading glasses previously used were not necessary for



close work (He had not received orchic extract from March 19 to Oct 14, 1941 and at the latter date was recovering from another cold)

By Feb 25, 1942 the patient, who had received but one injection of orchic extract in over eleven months (that on Oct 14, 1941), showed visual acuity for distance unchanged. However, the amplitude of accommodation was 25 diopters, there was slight enlargement of the blindspot in each eye, and the fields were narrower for colors than on Oct 23, 1941.

On April 6, 1942, visual acuity in each eye was 20/20 with correction, and the amplitude of accommodation measured between 275 and 30 diopters. The eyegrounds showed no pathologic change. However, the blindspots were still slightly enlarged (4 degrees downward), and the visual fields were somewhat narrower for red and green than on Oct 23, 1941. (By April 6, 1942 he was recovering from six weeks of grip and had received but one injection of orchic extract in more than a year.)

#### COMMENT

These patients were treated with injections of the orchic extract for periods varying from seventeen months to two and one-half years. An occasional complaint was made of pain at the site of injection, but there were no untoward symptoms with doses below 2 cc. This dose caused syncope in 1 patient. The dose of 1 cc. seemed ample.

The addition of acetylsalicylic acid, brewers' yeast and cod liver oil occasioned by grip and tonsillitis, which arose during the periods of study, can in no way be responsible for the favorable ocular changes noted. In fact, examinations of the eyes made during convalescence from grip showed decreased visual acuity for distance and marked impairment of the amplitude of accommodation without pathologic change in the eyegrounds, also, the visual fields were noticeably contracted for form and color compared with those found prior to and subsequent to the intercurrent ailment. Removal of dental infections when present was not begun until the treatment with orchic extract was well advanced and definite ocular improvement had occurred.

One was impressed by a greater sexual stimulus after each injection of testosterone propionate, compared with a better subjective response after an injection of orchic extract, though the limited number of injections does not permit an appraisal of any effect on the ophthalmoscopic picture.

The studies of the visual fields were made with an improved Forster Perimeter, 5 mm test objects being used in determining contraction of the fields for form and 8 mm test objects in determining contraction of the fields for colors (except when otherwise stated) at a distance of 330 mm. The tangent screen studies were made on a Gruss tangent screen with 4 mm and 2 mm test objects at a distance of 1 meter, the illumination used was that from a 75 watt Mazda lamp.

#### SUMMARY

Observations on 4 patients having eunuchoid skeletal measurements, one of them with eunuchoidism, another with eunuchoidism and a pituitary tumor, treated with injections of an orchic extract showed subjective improvement with a feeling of well-being and loss of fatigue. Before treatment all showed decreased visual acuity of more or less marked degree and diminished amplitude of accommodation. The eyegrounds showed changes ranging from hyperemia and postneuritic signs to complete decoloration of the optic nerve heads. Usually some vascular disease was present either in the form of premature arteriosclerosis or in that of absence of arterioles and capillaries. The visual fields were contracted, especially for colors (red and green), and in 2 cases there were central scotomas for colors. Usually there was diminished dark adaptation. During this therapy definite improvement was noted in the visual acuity for distance and in the amplitude of accommodation.



The pathologic changes in the eyegrounds disappeared, and later these showed normal, well colored and well defined optic nerve heads with little or no vascular abnormality. Dark adaptation returned to normal. The contraction of the visual fields for form and colors was definitely reduced, in some cases to normal.

Encouragement to publish the limited number of cases has come through some improvement with this therapy already noted in 3 other patients who have been observed from two to four months, an insufficient period for a report. The conditions treated have been (1) genuine syphilitic atrophy of the optic nerve, (2) optic atrophy associated with a pituitary adenoma and (3) retinitis pigmentosa.

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Dr Ervin Torok's ophthalmologic clinic cooperated in this work, especially Dr Joseph J. Fried of Dr Torok's staff, who made numerous ophthalmologic examinations and collaborated extensively, Dr A. Sumner Price, director of the laboratory, the consultants quoted and Drs N. B. Martin, Barnard Robbins, Antonette Raja and Franklin V. Sunderland gave helpful cooperation in the medical clinic.

# ACQUIRED HEMOLYTIC ANEMIA

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The anemia produced by accelerated disintegration of red blood cells leading to jaundice, increased excretion of urobilinogen and moderate splenomegaly often is accompanied by morphologic alterations of the red cells and usually is classified as hemolytic anemia. In a few instances the process may be truly hemolytic in the strict meaning of the word. However, in a majority neither the mechanism of the destruction of the red cell nor the fate of its stroma is known. I shall therefore employ the word "hemolysis" in its loose, hematologic rather than in its narrower, immunologic meaning throughout this discussion unless a clear distinction is specified.

I have observed a number of patients presenting hemolytic icterus of unknown cause with an acute or a subacute course similar to those whose cases were reported earlier by Widal and by Chauffard and their associates. In addition I have records of a number of patients with chronic acquired hemolytic anemia of unknown cause whose disease began acutely and followed a course characterized by continuous increased hemolysis and by recurrent severe crises of hemolysis similar to those seen in acute acquired hemolytic anemia.

Acute hemolytic anemia probably was first reported by Mackintosh and Cleland<sup>1</sup> in 1902. A few years later it was accurately described by Widal, Abram and Brulé<sup>2</sup> and was given the name "acquired hemolytic icterus" to differentiate it from the congenital type of hemolytic icterus, which had been described accurately by Minkowski<sup>3</sup> a few years earlier. Chauffard<sup>4</sup> had discovered the diminished osmotic resistance of the red cells and also the lessened diameter of the erythrocytes in congenital hemolytic anemia a short time before Widal's studies of acquired hemolytic icterus were published. Widal, Abram and Brulé<sup>5</sup> a year later reported autoagglutination of the red cells in the acquired type of the disease. Chauffard and Troisier<sup>6</sup> also studied the blood of a patient with the acute type of acquired hemolytic anemia and found that the serum contained an isohemolysin for normal erythrocytes. They, therefore, gave the name "acute hemolytic anemia" to the malady. During the years between 1907 and 1915 a number of discussions of acquired hemolytic anemia appeared in the French medical journals. Brulé<sup>7</sup> in 1922 reviewed the whole subject up to that date and pointed out

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1 Mackintosh and Cleland, cited by Sterner, L. G. Ein Fall von akuter hamolytischer Anämie von Ledererschen Typ, *Acta pædiat* **28** 196, 1940

2 Widal, F., Abram, P., and Brulé, M. Differentiation de divers types d'ictères hémolytiques par le procédé des hématies déplasmatisées, *Presse med* **15** 641, 1907

3 Minkowski, O. Ueber eine hereditäre, unter dem Bilde eines chronischen Ikterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affection, *Verhandl d Kong f inn Med* **18** 316, 1900

4 Chauffard, M. A. Pathogénie de l'ictère congénital de l'adulte, *Semana méd* **27** 25, 1907

5 Widal, F., Abram, P., and Brulé, M. L'autoagglutination des hématies dans l'ictère hémolytique acquis, *Compt rend Soc de biol* **64** 655, 1908

6 Chauffard, M. A., and Troisier, J. Anémie grave avec hémolysine dans la sérum, ictère hémolytique, *Semana med* **28** 94, 1908

7 Brulé, M. Recherches sur les ictères, Paris, Masson & Cie, 1922

the confusion which had resulted from the frequent failure to differentiate between hemolytic icterus with anemia and icterus of other types with anemia. Widal and Abram<sup>8</sup> in 1928 summarized the earlier reports and recorded their views concerning the mechanism of the disease. It is of interest that they did not seem to be aware of the presence of normal agglutinins and agglutinogens in human blood at that time. Thus there was some doubt concerning the significance of the autoantibodies and isoantibodies in the serum of the patients observed earlier by Widal, Abram<sup>8</sup> and Biule<sup>5</sup> and by Chauffard and Troisier<sup>6</sup> until the results of later studies fortunately confirmed their original observations.

I observed a patient with acute hemolytic anemia in 1916 and made a diagnosis of acquired hemolytic icterus. The patient recovered after splenectomy. Although the resistance of the red cells was normal, no studies to demonstrate autoantibodies in the blood of that patient were made.

In 1922 Eppinger<sup>9</sup> presented a summary of his studies of hemolytic anemia. He reported in detail 4 cases of acute hemolytic anemia which he had observed. Each of the patients was cured by splenectomy. All of them had increased hypotonic fragility of the red cells, and each was operated on while the anemia was profound. Eppinger discussed the problem of autoantibodies and isoantibodies but, apparently, was skeptical of the importance of these in the genesis of the malady, although he stated he had made no studies to determine their presence in his patients. The disease was reported by Lederer<sup>10</sup> and by Moschcowitz<sup>11</sup> in 1925. Neither of these authors seemed to be aware of the extensive literature on acquired hemolytic anemia. Davidson<sup>12</sup> in 1932 and Giordano and Blum<sup>13</sup> as late as 1937 described, as a new feature, the phenomenon of autoagglutination in this disease.

Meulengracht<sup>14</sup> discussed the disease briefly in 1938. He was aware of Eppinger's<sup>9</sup> report, but he did not mention the disease as Lederer's anemia. He was of the opinion that acute hemolytic anemia was of varied causation and not a true disease entity, and therefore he did not discuss the disease fully.

The recent report by Dameshek and Schwartz<sup>15</sup> contained a review of the reported examples of acute hemolytic anemia and an attempt to elucidate the importance of the hematologic phenomena in accordance with their experimental and clinical observations. They were able to find references to about 100 cases of acquired hemolytic anemia of varied causation which had been reported since 1907 under an array of different names. Their article contained an extensive bibliography, a comprehensive summary of the clinical and hematologic features of the disease and a discussion as to the proper nomenclature.

8 Widal, F., and Abram, P. Les ictères, in *Nouveau traité de médecine*, Paris, Masson & Cie, 1928, vol. 16, p. 263.

9 Eppinger, H. Die hepato-renalen Erkrankungen, in Langstein, L., and others. *Enzyklopaedie der klinischen Medizin*, Berlin, Julius Springer, 1920.

10 Lederer, M. A Form of Acute Hemolytic Anemia Probably of Infectious Origin, *Am J M Sc* **170** 500, 1925.

11 Moschcowitz, E. An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries, *Arch Int Med* **36** 89 (July) 1925.

12 Davidson, L. S. P. Macrocytic Haemolytic Anemia, *Quart J Med* **25** 543, 1932.

13 Giordano, A. S., and Blum, L. L. Acute Hemolytic Anemia (Lederer's Type), *Am J M Sc* **193** 786, 1937.

14 Meulengracht, E. Acquired Hemolytic Jaundice, in Downey, H. *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, p. 2314.

15 Dameshek, W., and Schwartz, S. O. Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), *Medicine* **19** 231, 1940.

They preferred the designation "acute hemolytic anemia" to the name "acquired hemolytic icterus" first used by Widal. I have followed their nomenclature at times in this paper simply to avoid confusion. However, I am convinced that a chronic type of the disease, and a recurrent form also, occurs more frequently than has been reported and therefore that the name "acquired hemolytic icterus" should be retained, with the terms "acute" and "chronic," as the better designation of the disease.

The 12 patients whose histories I am recording at this time were observed subsequent to 1916. Since I was, at that date, familiar with the reports of Widal and Chauffard, it is not likely that I failed to recognize the disease when I observed it. Thus I believe the disease is of relatively rare occurrence.

#### REPORT OF CASES

**CASE 1**—A woman about 25 years of age entered the Johns Hopkins Hospital, in Baltimore, in the spring of 1916, complaining of weakness. She had been losing strength for several weeks and had become very pale. Her previous history and the family history were unimportant. No other member of her family had had a similar disease.

At physical examination there was fever with a temperature above 102 F, as well as extreme pallor and deep jaundice. The spleen was slightly enlarged.

The hemoglobin content was about 30 per cent, and the erythrocyte count was 1,750,000 per cubic millimeter. There was moderate leukocytosis. The urine contained bile and increased amounts of urobilinogen. The osmotic resistance of the erythrocytes was normal. There was at that time, some doubt as to whether the patient had a hemolytic crisis in the course of congenital hemolytic icterus or had acquired hemolytic icterus.

Her condition did not improve after several transfusions. Soon a series of convulsions developed. Her condition became critical, and as a last resort the spleen was removed. About the tenth day she began to have fever again. An abscess under the left side of the diaphragm was opened and drained. The patient eventually recovered completely.

Her blood contained dark-staining microcytes which we would now call spherocytes, although at that time they were classed simply as microcytes.

**CASE 2**—C. M., a white girl of 15 years, was first seen on May 7, 1934. She complained of blotching of the skin, chiefly over the arms and legs, of three months' duration. These blotches were irregular and purplish red and usually followed fatigue or exposure to cold. They appeared from one to a dozen times a day.

Her past history was irrelevant, except that she had seasonal hay fever. Menstruation had begun a year previously, and the interval and the amount of flow were irregular.

Her father had advanced otosclerosis, and her mother had asthma and hay fever. There were no siblings and no history of anemia in the family.

Physical examination showed the girl to be normal except for the cutaneous manifestations mentioned.

About two weeks later, the blotching of the skin was more marked, and she complained of fatigue and extreme sensitivity to cold. At this time the peculiar dappled blotching of the skin was pronounced over the face, neck, arms and legs. Her temperature was 99.2 F. The results of physical examination were again negative. The skin regained its normal appearance after the patient had remained a short time in a warm room.

On May 22 the urinalysis gave normal results. The hemoglobin content was 57 per cent. The erythrocyte count was 2,520,000. The leukocyte count was 9,150. The stained smear was normal except for hypochromia and slight anisocytosis. From this time on there was constant fever, the temperature usually reaching 102 F daily. There was also increasing prostration.

On June 2 the right ear became painful, and a few drops of serous fluid were obtained by myringotomy. The erythrocyte count was 3,200,000. The hemoglobin content was 59 per cent, and the leukocyte count was 12,500. The icteric index was 8. The platelet count was 165,000 per cubic millimeter. Agglutination tests for typhoid-paratyphoid and Malta fevers were negative.

On June 4 the stools were dark, and the urine was coffee colored but contained no hemoglobin. There were gastrointestinal distress, occasional vomiting and tympanites.

On June 6 there was no occult blood in the stools. The hemoglobin content was 43 per cent. The erythrocytes were not abnormally fragile, hemolysis began in a 0.48 per cent

saline solution and was complete in a 0.34 per cent solution. The reticulocyte count was 12 per cent. A blood culture taken five days earlier was negative.

On June 8 the hemoglobin content was 31 per cent, the erythrocyte count was 1,310,000 and the leukocyte count was 14,800, with neutrophils 58 per cent, lymphocytes 35 per cent and the remainder normally distributed. The icteric index was 22.8. The Wassermann reaction was negative. The clotting time of the blood was eight minutes. The urine contained a heavy trace of albumin and a few hyaline casts but no bile. The temperature was 104.6 F. The pulse rate was 120 and the respirations were 30 per minute. The skin and scleras were markedly icteric. There were no petechiae. The gums and the throat were normal. The lymph nodes were not enlarged. A loud systolic murmur was heard at the cardiac apex. The spleen and the liver were not felt. The patient's blood belonged to group II (AB). Her blood contained an autoagglutinin to her own erythrocytes and to all cells of group II. Her serum did not agglutinate her father's erythrocytes, and his blood was of group IV. She was given 500 cc of his blood without reaction. She seemed better the next day, but her fever remained high.

On June 10 the hemoglobin content was 30 per cent, and the erythrocyte count was 1,400,000. One drop of the patient's venous blood was placed in 2 cc of 1 per cent citrate solution and shaken. Hanging-drop preparations of this blood specimen showed rapid and marked autoagglutination. The patient's blood serum on this date also agglutinated her father's erythrocytes (group IV [O]) in fifteen minutes and also group IV (O) cells from 2 normal persons and group II (AB) cells from a normal person. No autohemolysis was present. Stained smears of the blood showed numerous spherocytes and macrocytes and a few normoblasts.

The patient died on June 12. Her temperature reached 106 F by axilla, and her pulse and respirations became very rapid before death.

*Autopsy*—(The embalmed tissue was not placed in fixing solution for several days, so that the stained microscopic sections were not very satisfactory.) The liver weighed 1,800 Gm. The cut surface had a coarse granular appearance. The parenchyma was firm and dark red.

The spleen weighed 240 Gm. It was dark red and firm. The cut surface was granular and cut with a grating sensation.

There were marked gross changes of all lymph nodes of the abdominal cavity. These nodes were very firm and dark red. There was a cluster of nodes, varying in size from a walnut to a pea, located at the hilus of the spleen. A similar cluster of nodes was located about the celiac plexus. The cut surfaces of these nodes had the appearance of normal liver tissue, thus resembling hemolymph nodes. About two hundred of these nodes were scattered through the mesentery and the retroperitoneal areas. The mediastinal and superficial lymph nodes were unchanged.

The chief alterations observed in sections of the spleen were diffuse congestion of the pulp spaces with moderate compression of the blood sinuses. The majority of the sinuses were empty and lined with large endothelial cells. A number of these endothelial cells contained varying amounts of hemosiderin. The malpighian corpuscles were less numerous than normal.

The enlarged lymph nodes found in the mesentery all exhibited greatly widened sinuses, which were filled with lymphocytes and macrocytes.

Sections of the kidneys showed enlarged glomeruli, with partial occlusion of the capillaries by swollen endothelial cells.

The liver showed small areas of necrosis.

CASE 3—E. A., a white married woman 45 years of age, was admitted to Saint Mary's Long Beach Hospital, Long Beach, Calif., on July 22, 1940 and died on Aug. 30, 1940.

Her illness began about four days before admission with pain in the epigastrium and on the right side of the back over the lower ribs. The pains continued, and two days later she vomited and was found to have fever.

The past history was irrelevant. So far as she knew, no member of her family had had a similar illness or chronic jaundice.

She was pale and icteric. The skin was otherwise normal. The throat and the gums were normal. The scleras were icteric. The lymph nodes were not enlarged. There was a soft systolic murmur over the heart. The abdomen was not tender, and no masses or viscera were felt. On July 22 the Wassermann and Kahn reactions were normal. The hemoglobin content was 16 per cent. The erythrocyte count was 795,000, and the leukocyte count was 35,600 (not corrected for normoblasts). There were 74 per cent neutrophils, and the proportion of the other cells was normal. There was anisocytosis with macrocytes and microspherocytes and many diffusely basophilic erythrocytes. Many normoblasts were present. The icteric index was 25.

The fever remained between 101 and 104 F, and from her admission until August 16 she received eleven transfusions. Following each of these, the fever became higher and the icterus more pronounced. On July 29, the erythrocyte count was 2,080,000, the leukocyte count was 14,600 and the hemoglobin content was 25 per cent.

The fragility of the erythrocytes was normal (initial hemolysis at 0.46 per cent and complete hemolysis at 0.32 per cent) on several occasions. The patient's blood belonged to group O. No autoagglutinins, autohemolysins, isoagglutinins or isohemolysins were demonstrated at room temperature, although isoagglutinins and autoagglutinins were present when the blood was in the ice box.

The urine and the stool contained bile.

The spleen was removed August 16. It weighed 510 Gm. After this operation the patient improved rapidly. On August 21 the hemoglobin content was 52 per cent, and the erythrocyte count was 3,140,000. A few days later, chills and fever developed, and the patient failed rapidly. She died on August 30.

*Autopsy* (Aug. 30, 1940).—An abscess containing about 75 cc of pus was present below the left side of the diaphragm. Adhesions were present about the gallbladder and adjacent viscera. The liver was moderately enlarged and firm. The bone marrow and the lymph nodes were normal.

The spleen (removed at operation) weighed 510 Gm. The organ was firm and was normal in shape. It was grayish purple. Its cut surfaces were dark red with prominent, irregularly shaped grayish foci, less than 1 mm in diameter, representing accentuated normal architectural markings.

On microscopic examination the splenic follicles were small and distinct, with no evidence of fibrosis. The sinusoids were almost empty and were prominent, their endothelial cells being large. Hyperplasia of the reticular system was marked. There was congestion of the pulp, but there was noticeable destruction of red blood cells, many disintegrating red cells being present and much amorphous debris being found. There was no evidence of leukemia.

**CASE 4**—M. S., a white woman 27 years old, was admitted to the Cedars of Lebanon Hospital, in Los Angeles, on Jan. 11, 1941 and was discharged on Feb. 10, 1941.

In July 1940 she had on her arms and legs a few areas that looked like blisters. The larger ones were about 3 cm in diameter. These broke and discharged and then disappeared and have not recurred. At that time she was given a few doses of a sulfonamide compound, and she thinks she became anemic. In October 1940 she was told that her blood counts were normal, and she felt well. About two weeks before admission she had headaches and became weak. She could not walk without staggering. She had pounding in her ears on the least exertion. A few days later she noticed that her skin was yellow. During this time she took no medicine except a few tablets of acetylsalicylic acid.

At examination, the temperature was 101 F, the pulse rate was 100 and the blood pressure was 105 systolic and 55 diastolic. She was pale, and the skin and the scleras were moderately icteric. There were no petechiae. The mucous membranes were normal except for pallor. The lymph nodes were not enlarged. The spleen was easily felt. The liver was not enlarged.

The urine was normal and contained no bile. Urobilinogen was present (1/100). The icteric index was 54. The erythrocyte count was 1,480,000. The hemoglobin content was 26 per cent and the leukocyte count was 5,100. There were 77.5 per cent neutrophils and 20.5 per cent lymphocytes. There was moderate anisocytosis. No spherocytes were seen. There were numerous normoblasts. The fragility of the erythrocytes to hypotonic salt solutions was normal, hemolysis began at 0.45 per cent and was complete at 0.3 per cent. The gastric analysis showed 35 per cent free hydrochloric acid and 65 per cent total acidity. The bleeding time (Duke method) was two minutes and thirty seconds. The Wassermann reaction with serum was negative. The blood did not show the bands of a porphyrin. The patient's blood belonged to group AB. The serum produced no hemolysis or agglutination when set up with the patient's own erythrocytes either in the ice box or at room temperature. There was also no hemolysis at 80 C with any normal type serums used against the patient's cells. Furthermore, heated normal serums reactivated with guinea pig complement against her cells produced no hemolysis. The serums of groups B and O and cells of the patient showed hemolysis and strong agglutination.

In the hospital the patient's temperature varied from 101 to 106 F. She was gravely ill, and in spite of numerous transfusions her condition did not improve. The hemoglobin content reached 50 per cent before operation. On Jan. 20, 1941 the spleen was removed. Just after the operation the platelet count was 330,000 per cubic millimeter. Her temperature reached normal two days after operation.

On January 22 the hemoglobin content was 60 per cent, and the leukocyte count was 10,000. On January 31 the patient aborted a 2 month fetus. She was given three transfusions after operation, and her condition slowly improved, although mild blood changes were still present in August 1942.

The spleen measured 15 by 7 by 4 cm. At the hilus were several small accessory spleens. The veins were thin and smooth. The cut surface was fleshy and deep purple. Scattered through the pulp were numerous small nodules, irregular in shape and size but slightly larger than malpighian bodies, and measuring up to 3 mm in diameter. The gross specimen was reminiscent of a spleen showing Hodgkin's disease.

The microscopic observations on the spleen were as follows. The capsule was normal. The trabeculae were normal. The blood vessels were dilated, and there were a few intravascular thrombi. The pulp spaces showed unusually dilated sinusoids, giving the impression of intense, fairly acute and active hyperemia. The distinction between sinusoids and pulp was poorly defined, and in the pulp there was moderate reticuloendothelial hyperplasia. The majority of the follicles were normal. Some were altered to form the gray nodules seen in the gross specimen. These showed hyperplasia and infiltration with lymphocytes, polymorphonuclear cells and a few plasma cells. There were a few multinucleated cells in the areas of newly formed stroma. There were a few hemorrhages near the follicles. There was little erythrophagocytosis. Splenic extracts were made, but no hemolysin was demonstrated. Stains of the spleen for iron showed a large increase.

CASE 5—J. B., a white woman 32 years old, was admitted to Saint Mary's Long Beach Hospital, Long Beach, Calif., on Feb. 10, 1942 and died on Feb. 14, 1942.

She had had heart trouble for many years. The acute illness for which she was admitted to the hospital began ten days previously with generalized pains and fever. There was also considerable cough at first. During the illness the urine was dark. During the past twenty-four hours the skin had become yellow.

There were pallor and moderate icterus. There were no petechiae and no enlarged lymph nodes. The pulse rate was 110 per minute. The temperature was 101 F. The blood pressure was 120 systolic and 60 diastolic. There were sibilant rales in each lung. The heart was enlarged to the right and to the left. The first sound was loud at the apex, and there were a loud presystolic murmur and a short, loud systolic murmur. The edge of the liver was 4 cm. below the left costal margin.

On February 11 the hemoglobin content was 7.53 Gm. The erythrocyte count was 1,750,000. The leukocyte count was 48,100. There were a few normoblasts. There were 84 per cent neutrophils and 12 per cent lymphocytes. A stained smear showed numerous macrocytes and microspherocytes. The icteric index was 79. The patient's serum clumped her own cells and the cells of all four normal types. (Her father's serum also agglutinated cells of all normal types.)

The patient's temperature remained at 102 F., and the pulse rate ranged from 180 to 250 per minute. On February 14 the hemoglobin content was 5.0 Gm., the erythrocyte count was 1,100,000, the leukocyte count was 61,400 and the platelet count was 520,000 per cubic millimeter. The erythrocytes were not abnormally fragile to hypotonic salt solution, hemolysis began at 0.48 per cent and was complete at 0.38 per cent. The urine showed some albumin and many casts but no hemoglobin. The patient died. Permission for an autopsy was not obtained.

CASE 6—D. H., a white man 67 years old, was seen in consultation on Dec. 31, 1941. He had been well until the age of 58 years, when he had a coronary occlusion followed by atrial fibrillation, which has persisted. About three years prior to examination glycosuria was noted and was thereafter easily controlled with insulin. In late September or early October 1941 he began to show pallor and tired easily. During November he felt fairly well, but his friends noticed that he was very pale. Early in December he was exhausted and noticed that his urine was dark. He had no pain. At that time the erythrocyte count was 3,200,000 per cubic millimeter. The hemoglobin content was 60 per cent.

On December 14 there was marked jaundice. The urine was dark but was not tested for bile. The pulse rate was 80 per minute. There were no petechiae. The spleen and the liver were not felt. There was no fever. The icteric index was 80. The erythrocyte count was 2,700,000 and the leukocyte count was 7,600. The hemoglobin content was 47 per cent. There were many poikilocytes and marked anisocytosis. There was marked basophilic stippling. No definite microspherocytes were seen. There were many reticulocytes. The differential count was normal.

From December 17 to 31 he received five transfusions. His temperature rose gradually from 100 F. to 102 F. to 103 F. daily. There was no bile in the urine. The icteric index was 20. His Wassermann reaction was negative.



On December 31 he was extremely ill. The hemoglobin content was 28 per cent. The erythrocyte count was 1,500,000 and the leukocyte count was 6,300. There were 90 per cent neutrophils. The pulse rate was 140. His temperature was 103.6 F. The fragility of the erythrocytes to hypotonic salt solution was normal. His serum did not agglutinate or hemolyze his own or other erythrocytes of the same type as his. Nothing new was found by physical examination except that the tip of the spleen had become palpable. A blood culture was negative.

The diagnosis seemed clearly established except that the absence of spherocytes had not been noted in any previous case. Splenectomy was considered, but because of his age and the complicating diabetes mellitus and heart disease the operation seemed too hazardous. He was given numerous small transfusions. His jaundice slowly disappeared, and his blood became normal.

A few months later, however, pallor and jaundice reappeared, and the spleen again became palpable. The anemia became marked, and anisocytosis with macrocytosis and microcytosis was present. Only a few microspherocytes were ever present in stained films. The osmotic fragility of the erythrocytes was normal, and no autoagglutination was observed.

His condition became critical, and repeated transfusions only increased the icterus without influencing the anemia. The spleen was removed. Following this, the anemia improved, but secondary hyperthrombocytosis developed with multiple venous thromboses, from which he died.

**CASE 7**—A white woman 29 years old was admitted to the Los Angeles County Hospital on March 15, 1942. She complained that she had suffered from chills, fever, weakness, jaundice, headache and breathlessness for ten days. The illness began about two weeks before admission, when her color was said to be peculiar, and the whites of her eyes became yellow. Ten days before admission she was drenched by a cold rain, and that night she began to have chills and fever. She also had cough and a pounding headache. On March 18 she began to notice breathlessness. The jaundice became deeper, and nausea and vomiting developed.

She had had no serious illnesses previously. Her menstruation was normal. She had had four pregnancies. The first ended at six months, the second at six weeks. The last two resulted in normal births at term. A positive Wassermann reaction was present in 1939, and she received injections in the hips and veins. The last treatment was in November 1941. No other member of her family was known to have jaundice or anemia.

Her temperature was 102 F. The pulse rate was 120. The blood pressure was 130 systolic and 80 diastolic. There was marked icterus of the skin and of the scleras, and there was marked pallor. There were a few small hemorrhages in each fundus. There were no petechiae. The lymph nodes were not enlarged. The edge of the liver was about 6 cm. below the costal margin. The tip of the spleen was just felt.

The hemoglobin content was 22 per cent. The red cell count was 880,000 and the white count was 28,900 per cubic millimeter. There were 30 per cent reticulocytes. The differential count was normal. There were many macrocytes and normoblasts and many microspherocytes. The icteric index was 56. The urine contained a large amount of urobilin. The stool was very dark but contained no blood. With hypotonic saline solutions the red cells showed beginning hemolysis at 0.82 per cent and complete hemolysis at 0.28 per cent. There were no demonstrable autoantibodies or isoantibodies.

In the hospital the temperature remained between 101 and 104 F. The patient was given numerous transfusions. Her blood picture and general condition improved. On April 19 her symptoms increased and her anemia began to increase.

On April 22 the hemoglobin content was 22 per cent, the red cell count was 1,100,000 and the white cell count was 8,700. The stained films of blood showed many macrocytes, microcytes and microspherocytes.

Her condition became worse rapidly, and on April 24 her spleen was removed. It was large, and sections showed some areas of necrosis. There was some phagocytosis. The pulp spaces were markedly congested.

No stones were present in the gallbladder. There were a number of enlarged lymph nodes, some as large as a walnut, along the greater curvature of the stomach.

On May 6 some fluid with inflammatory cellular content was removed from the left pleural cavity. Following this, the patient's condition improved.

On June 15 the hemoglobin content was 44 per cent, the red cell count was 2,370,000 and the white cell count was 14,400. There were numerous microspherocytes in the stained film. The icteric index was 13.

On July 13 the hemoglobin content was 69 per cent, the red cell count was 3,490,000 and the white cell count was 7,800. The stained smear showed marked anisocytosis with many macrocytes and microcytes and numerous microspherocytes. The fragility of the red cells to hypotonic saline solution was normal.



CASE 8—J S, a white man 44 years old, was admitted to the Los Angeles County Hospital on Oct 13, 1941 and died on Nov 3, 1941

He complained of weakness, breathlessness on exertion, yellow skin and pallor of three months' duration. He stated that during the past five years he had had several episodes of jaundice and weakness with severe anemia. The first one followed a series of colds in the head. He was in a hospital at that time and was given injections of liver extract. Between the various attacks of jaundice he recovered and returned to work. The last attack before the present one was eighteen months ago.

About ten days before admission he had severe pain in the left upper quadrant of the abdomen, associated with pain on breathing.

Five years ago he had a number of attacks of pain in the right upper quadrant of the abdomen and was told he probably had gallstones. He never had clay-colored stools during any of these illnesses, although the urine was often quite dark. During the past three years his attacks of weakness, jaundice and anemia have not been associated with pain in the right upper quadrant.

His past history is otherwise irrelevant. So far as he knows, none of his family has had a similar illness.

The pulse rate was 78 per minute, the temperature was 102.4 F, the blood pressure was 140 systolic and 50 diastolic. The patient seemed acutely ill. There was marked pallor, and the skin and the scleras were icteric. The tongue was not smooth. There was no abnormal enlargement of the lymph nodes. The lungs were normal. There was a loud systolic murmur over the body of the heart. The edge of the liver was felt about 6 cm below the costal margin. The spleen was felt about 4 cm below the costal margin. The liver was tender. The skin was normal except for the presence of a shallow ulcer, about 1 by 1.5 cm, on the lower part of the left leg.

On October 13 the erythrocyte count was 1,030,000, and the leukocyte count was 47,000 per cubic millimeter. The hemoglobin content was 22 per cent. There were many normoblasts. There was marked anisocytosis with many small, dark microspherocytes.

On October 14 the hemoglobin content was 4 Gm (25 per cent), the erythrocyte count was 960,000, and the leukocyte count was 49,100 but was 22,300 when corrected for normoblasts. There were 23 per cent reticulocytes. There were 64.5 per cent neutrophils, 21 per cent lymphocytes, 11 per cent monocytes and 3.5 per cent other cells. There were 119,000 platelets per cubic millimeter. The smear showed anisocytosis with some macrocytes and numerous hyperchromic microspherocytes. The icteric index was 120. The urine contained large amounts of bile and urobilinogen. The patient's blood was type O (Moss group IV), but his serum agglutinated the cells of all donors and it also agglutinated his own red cells. Tests for fragility of his cells were set up, hemolysis began at 0.8 per cent and was not complete until 0.26 per cent hypotonic salt solution was reached.

On October 25 the patient was extremely ill. His temperature varied between 101 and 103 F. The nonprotein nitrogen amounted to 70 mg per hundred cubic centimeters. The icteric index was 96. The serum albumin was 3.19 per cent and the serum globulin was 3.1 per cent. The prothrombin content was 60 per cent of normal. The hemoglobin content was 36 per cent. Cholecystotomy was done, and gallstones were removed. On October 29, following the removal of the gallstones, the patient's condition became critical, and splenectomy was performed. At that time his erythrocyte count was 900,000.

On October 31 the patient was gravely ill. His temperature was 103 F, his pulse rate, 132 per minute. On November 1 the icteric index was 240. On November 3 the patient died.

After the spleen was removed, no further autoagglutination was noted during blood counts, and the resistance of the red cells returned to normal at the end of forty-eight hours.

Blood specimens from three sons of this patient were examined. The erythrocytes of none of them showed any increased fragility in saline solutions. The patient's brother's erythrocytes also showed no increase of fragility. The patient's Wassermann and Kahn reactions were negative.

Before each operation the following tests were made at room temperature:

	Patient's Serum	Group O Serum	No Serum
Patient's erythrocytes in 0.85 per cent sodium chloride solution	No hemolysis at 4 and 16 hr	No hemolysis at 4 and 16 hr	Moderate hemolysis
Patient's erythrocytes in 1.0 per cent sodium chloride solution	No hemolysis	No hemolysis	Slight hemolysis
Group O erythrocytes in 0.85 per cent sodium chloride solution	No hemolysis	No hemolysis	No hemolysis

The patient's serum agglutinated his own red cells and red cells of all normal types, but no hemolysins could be demonstrated. The spleen weighed 600 Gm and was purplish red.

The pulp spaces were packed with red cells, and the splenic sinuses were obliterated. There was some hemosiderosis, and a few macrophages contained erythrocytes. No other lesion of importance was found at autopsy.

**CASE 9—A C**, a white girl 17 years old, was admitted to the Hospital of the Good Samaritan, in Los Angeles, on Dec 8, 1939 and was discharged on Jan 29, 1940.

At the age of 7 years she began to have attacks of severe pain in the upper abdominal region. At that time the spleen was enlarged. With the attacks she had nausea and vomiting. Often several months intervened between the attacks of pain. During these years she was often quite anemic, and her mother thought there was some relation between the attacks and the anemia. At one time the hemoglobin content was as low as 36 per cent. She had some fever with each of the attacks. She was given three transfusions during those years. She never had abnormal bleeding of any type. About three weeks before the present admission she had a severe attack of pain in the upper part of the abdomen, and in a few days her skin was quite yellow. She had a high fever and was very ill.

The tonsils had been removed. She had had measles, mumps and pertussis. Her menstrual history was normal. There were no siblings, and the family history revealed no similar disease, although her mother had had gallstones removed.

Physical examination showed a patient strikingly pale and deeply icteric. She was acutely ill and moderately delirious. Her temperature was 100 F. The blood pressure was 100 systolic and 70 diastolic. There were no petechiae. The lymph nodes were not enlarged. The liver was not enlarged. The soft edge of the spleen was felt just above the umbilicus.

On December 8 she had a convulsion, and on December 9 she had three more convulsions. The jaundice was marked. The urine contained bile and a heavy trace of albumin. The hemoglobin content was 66 per cent. The erythrocyte count was 4,000,000. The leukocyte count was 11,000. There were 87.5 per cent neutrophils. The icteric index was 700. The sedimentation rate was 12 mm in twenty-four minutes (normal, 120 minutes). The blood cholesterol amounted to 284 mg per hundred cubic centimeters. The Wassermann reaction was normal.

On December 11 the patient was intensely icteric. There was no bile in the stool. A roentgenogram of the abdomen showed a large spleen, a slightly enlarged liver, ten gallstones in the gallbladder and one in the region of the ampulla. Roentgenograms of the bones showed no changes of congenital hemolytic icterus. On December 15 the hemoglobin content was 30 per cent. The leukocyte count was 4,100 and the erythrocyte count 2,000,000. One normoblast was seen. Many spherocytes were present. The coagulation time was fifty-five minutes (Howell method). The icteric index was 160.

On December 18 the fragility of the erythrocytes to hypotonic saline solution was normal. No autohemolysins or autoagglutinins were demonstrated.

On December 21 cholecystotomy was performed. Ten stones were removed, and the common duct was probed. The icteric index was 74.

On December 26 the hemoglobin content was 67 per cent. On January 27 the icteric index was 30.

*Course of the Disease*—From December 9 to December 15 the hemoglobin content decreased from 66 to 30 per cent. During that time there was extreme hemolysis and, in addition, the stools were acholic from obstruction of the common duct.

During the first week in the hospital her fever was low, but from December 14 to January 10, 1940 she was delirious or comatose and her temperature varied from 102 to 104 F. Following this period, the hemolysis became less, the hemoglobin increased and the temperature returned to normal.

This patient has been observed on many occasions since the early part of 1940. On all occasions she was anemic and icteric, and the spleen was felt near the level of the umbilicus. The latest blood count at the time of writing was made in February 1942. The hemoglobin content was 52 per cent. The red cell count was 4,300,000, and the white cell count was 7,900 with 65 per cent neutrophils. There were large numbers of microspherocytes and a few macrocytes. The reticulocytes were 16 per cent.

**CASE 10—H I**, a Japanese girl 15 years of age, was first seen in October 1938. About two weeks previously she began to have jaundice. By December 27 the jaundice was deeper, and she was admitted to the hospital.

She had been well previously, although she had lost 10 pounds (4.5 Kg) in the past three months. Neither parent had had jaundice.

On admission her temperature was 99.4 F. The tonsils were large. The spleen and the liver were not felt. The hemoglobin content was 37 per cent. The red cell count was 1,380,000. The white cell count was 10,400. The color index was 1.4. The differential count was normal. There were many macrocytes and microcytes and numerous normoblasts. The

reticulocyte percentage was 84. The icteric index was 40. Hemolysis in hypotonic saline solutions began at 0.50 per cent and was complete at 0.40 per cent. The diameter of the red cells varied from 4 to 11 microns.

On Jan. 27, 1939 the spleen was removed because the patient was believed to have congenital hemolytic jaundice.

On March 27 the hemoglobin content was 77 per cent, and the white cell count was 8,600. The patient felt well, but she was still icteric.

On August 10 the icteric index was 260, the hemoglobin content was 41 per cent, and the white cell count was 15,150. There were numerous microcytes and normoblasts.

On Jan. 2, 1940 she was admitted to the Los Angeles County Hospital. She complained of weakness, nausea, vomiting and jaundice. She was found to have deep jaundice. Her temperature was 103 F. The edge of the liver was 5 cm below the costal margin. The red cell count was 980,000. The white cell count was 70,000 (uncorrected for normoblasts). Fragility tests with hypotonic saline solutions showed hemolysis beginning at 0.72 per cent and complete at 0.42 per cent.

Her temperature rose to 102 F or more each day. On January 14 the icteric index was 364.

On January 5 the hemoglobin content was 44 per cent, the red cell count was 1,660,000 and the white cell count was 82,150 (when corrected for normoblasts it was 16,680). The differential count was normal. With hypotonic saline solutions, hemolysis began at 0.72 per cent and was complete at 0.26 per cent. There were numerous macrocytes, normoblasts and spherocytes at all times, and the reticulocytes were greatly increased.

On January 22 tests for fragility of erythrocytes showed initial hemolysis at 0.84 per cent and complete hemolysis at 0.34 per cent. Approximately the same results were obtained ten days later. The patient continued to have fever daily. She was given three transfusions. On March 1 the red cell count was 2,500,000, the white cell count was 20,600 and the hemoglobin content was 70 per cent. The smear showed many macrocytes, normoblasts and spherocytes. The icteric index was 44. The urine contained bile and a large amount of urobilinogen.

On March 27 the patient had improved slowly. Her fever had nearly disappeared. The abdomen was searched for an accessory spleen or hemolymph nodes. None was found. The gallbladder was removed, and it was essentially normal but contained ten small soft pigment stones.

On June 14 the patient was icteric. The icteric index was 20. The hemoglobin content was 64 per cent. The red cell count was 2,820,000 and the white cell count was 9,550. The color index was 1.26. The reticulocyte percentage was 20.4. Five normoblasts were seen. The smear showed many macrocytes and numerous spherocytes.

Tests for autoagglutination and isoagglutination were not made at any time. However, since typing for transfusion was not difficult, one may assume that there was no isoantibody present.

**CASE 11**—F. F., a white woman 55 years old, was admitted to the Los Angeles County Hospital on Sept. 7, 1941. She complained of jaundice of eight months' duration.

Three years previously her gallbladder was removed, but no stones were found. Four months later the abdomen was again explored. Since then she had felt weak and run down.

Eight months before admission she became ill with fever, chills and jaundice, and these had been present at intervals up to the time of admission. She had vomited frequently and had had some abdominal pain during the past eight months. During that time she had seven blood transfusions to relieve her anemia.

Her father died of pneumonia and her mother died of renal trouble. She had six siblings living and well. None had jaundice. She had two children, aged 33 and 36, living and well.

Her appendix was removed at the age of 25 years. Afterward an ovarian cyst and the tonsils were removed, and a ventral hernia was repaired. She had a normal menopause at 41 years of age.

On physical examination her temperature was 102.2 F. The blood pressure was 130 systolic and 80 diastolic. She appeared chronically ill. She was pale and jaundiced. There were no petechiae, angiomas or enlarged lymph nodes. The heart and the lungs were normal. The edge of the liver was felt about 5 cm below the costal margin. The lower border of the spleen was palpable 8 cm below the costal margin.

On September 9 the hemoglobin content was 44 per cent, the red cell count was 2,360,000 and the white cell count was 14,100. There were 84 per cent neutrophils and 16 per cent mononuclear cells. The urine was loaded with pus and *Escherichia coli*. Her temperature was 104 F. Several stools were examined, and no abnormalities were noted. The icteric index was 28. The blood cholesterol amounted to 165 mg per hundred cubic centimeters. The prothrombin content was 75 per cent of normal. The bleeding time was one minute, the

clotting time was six minutes, the clot retraction was normal. Tests for fragility of red cells showed initial hemolysis at 0.56 per cent and complete hemolysis at 0.26 per cent.

On September 17 the hemoglobin content was 8.5 Gm, and the red cell count was 2,590,000. The hematocrit reading was 22 cc of packed cells per hundred cubic centimeters of blood. The volume index was 1.04. The mean cell volume was 88 cubic microns and the mean cell hemoglobin content was 34 micromicrograms. There were many macrocytes and spherocytes. The bone marrow was said to be consistent with the diagnosis of congenital hemolytic jaundice. Several blood cultures were negative. On October 21 the fragility test showed beginning hemolysis at 0.6 per cent and complete at 0.26 per cent. The Wassermann reaction was negative. The urine contained an excess of urobilinogen.

The patient's condition became steadily worse, and she was believed to have an obstruction of the bowel. On September 22 the abdomen was opened. There were many adhesions. Nothing of importance was visualized, and nothing was done. The postoperative course was stormy, but she recovered. Some ascites was present for several weeks and then disappeared.

On October 28 the hemoglobin content was 60 per cent, and the red cell count was 2,110,000. She had continuous pyuria and apparently pyelonephritis.

On March 8, 1942, the hemoglobin content was 50 per cent, the red cell count was 2,010,000 and the white cell count was 7,100. A differential count was normal. There were 10 per cent reticulocytes. The fragility test with hypotonic saline solutions showed initial hemolysis at 0.72 per cent and complete hemolysis at 0.26 per cent. The stained smear showed many macrocytes and microspherocytes. The icteric index was 13.

The patient went home but was readmitted to the hospital May 14. She complained of burning and frequency of urination. Her legs were slightly swollen. There was considerable pain in the left upper quadrant of the abdomen. Her blood pressure was 154 systolic and 92 diastolic. The spleen reached to the umbilicus. The liver was just felt. There was a blowing systolic murmur at the apex, but the heart was otherwise normal. There was slight jaundice.

The urine contained numerous pus cells, but no albumin or casts were found.

On May 15 the nonprotein nitrogen amounted to 40 mg per hundred cubic centimeters. The serum albumin was 4 per cent, and the serum globulin was 2.5 per cent. The icteric index was 25. An electrocardiogram was normal. The hemoglobin content was 51 per cent. The red cell count was 2,100,000. The white cell count was 8,400. The reticulocyte count was 23 per cent. The differential count was normal. The smear showed many macrocytes and microcytes and numerous microspherocytes. With hypotonic saline solution, hemolysis of the red cells began at 0.68 per cent and was complete at 0.28 per cent.

On June 8 the icteric index was 51. The urine was essentially normal, and it was believed that the pyelitis was cured.

On June 13 the spleen was removed. It weighed 680 Gm. Sections showed only marked congestion of the pulp spaces with obliteration of the sinuses. A few macrophages containing erythrocytes were seen.

On June 15 the hemoglobin content was 78 per cent, the red cell count was 3,560,000 and the white cell count was 11,800. A stained film showed numerous macrocytes and microcytes.

The patient continued to improve, but blood smears studied in August 1942 still showed the characteristic changes of the red blood cells. Thus the symptoms had been relieved, but the evidences of the disease in the altered appearance of the red cells still persisted.

CASE 12—H. S., a white woman 64 years old, was admitted to the Hospital of the Good Samaritan, in Los Angeles, on June 4, 1942. She complained of weakness, breathlessness and irregular beating of the heart.

She first noticed her illness about two years previously, when she began to have increasing weakness and nervousness. In January 1942 she became very weak and short of breath, and she noticed that her skin was pale. Numbness of the hands developed, and her gait was uncertain. She was given iron and injections of liver daily, but she did not improve.

During the two months prior to her admission to the hospital she had been given four transfusions without relief. About a month before, she noticed that her skin was yellow.

Physical examination showed nothing remarkable except pallor, moderate jaundice and a large spleen with the edge reaching to the level of the umbilicus. The spleen was not tender. There were no petechiae, no swelling of the gums and no enlarged lymph nodes. The deep and superficial reflexes were all normal. The sense of position and vibratory sense were normal.

The urine had a specific gravity of 1.017 and contained no sugar, a faint trace of albumin was present. Urobilinogen was positive in the dilution 1:130.

The hemoglobin content was 31 per cent. The red cell count was 1,600,000. The leukocyte count was 5,000, with a normal distribution of the cell types. There were moderate numbers of macrocytes and spherocytes. There were 24.4 per cent reticulocytes. The icteric index was 32. The hematocrit reading of the packed cell volume in a Sahli tube was 16 per cent.

The Wassermann reaction was negative. The patient's blood belonged to type IV (O). The van den Bergh test gave a negative direct reaction. With hypotonic saline solution, hemolysis began at 0.4 per cent and was complete at 0.3 per cent. In hanging drop preparations the patient's serum agglutinated her own red cells. No evidence of autohemolysis was present.

The patient had a low grade fever, with a temperature between 99 and 100 F.

On June 5, 1942 the hematocrit reading was 16 per cent with the Sahli tube. The reticulocyte count was 24.4 per cent, and the icteric index was 32.

On June 17 the spleen was removed by Dr. C. F. Sturgeon. It weighed 1,950 Gm. and measured 35 by 20 by 12 cm. It was soft and contained innumerable tiny gray areas, which were probably hyperplastic lymph follicles. Sections showed numerous malpighian bodies. The spleen was very cellular, and the pulp spaces were distended with blood.

On June 18 the hemoglobin content was 48 per cent.

On July 8 the hemoglobin content was 73 per cent, and the red cell count was 4,000,000. The stained film showed slight anisocytosis, but no microspherocytes were present. The icteric index was 9. The patient seemed entirely well, and her blood had returned to normal. At operation her gallbladder contained a few stones, but these were not removed.

#### RESUME OF OBSERVATIONS

The clinical features of the acute form of acquired hemolytic anemia have been very similar in all of the reported cases. In children the disease usually has had an abrupt onset with chills and fever and frequently has run its course in a week or ten days, or even less. In adults there was as a rule a period of variable duration marked by increasing fatigue, weakness and malaise. In a few cases this period was brief but most of our patients when questioned carefully recalled that their symptoms began insidiously a few weeks or even a few months before they consulted a physician. By that time the usual complaints were exhaustion, dizziness, anorexia, nausea, vomiting and often abdominal cramps. Some patients also complained of headache, breathlessness and faintness on exertion.

On the first examination pallor and jaundice were always present, and there was some fever. Following this period, the symptoms frequently became more severe rapidly. The temperature usually varied between 101 and 104 F. but was occasionally higher. Chills were frequently present. The anemia usually became profound. Jaundice increased, and the patient at times became delirious or even had convulsions. At this later period physical examination as a rule showed only jaundice, pallor and slight enlargement of the spleen and possibly of the liver. One patient presented a remarkable erythematous lesion of the skin. The stools were often dark owing to the presence of large quantities of bile pigment, and the urine also contained large amounts of bile and urobilinogen. In some patients, after a variable number of transfusions, the symptoms ameliorated and complete recovery took place. This result in the reported cases seemed to be especially frequent in children. In other patients transfusions produced intensification of the icterus and fever without any gain in hemoglobin, while in still other patients severe reactions to transfusion occurred. In some instances the patient's condition soon became critical, and splenectomy had to be performed as a life-saving measure.

The duration of the acute type of acquired hemolytic anemia has varied considerably. There was a fulminating type, especially in children, which ran its course in a few weeks or less, and there was a subacute type lasting from a month to three months or more. Since any separation into acute and subacute types is purely arbitrary, I have grouped these cases together as examples of acute acquired hemolytic anemia of unknown cause. In addition to this group I have observed a number of cases of a chronic type marked by acute hemolytic crises, often of extreme severity, and by marked instability of the hemolytic balance of the red cells but otherwise presenting the same hematologic features as the

acute type, although somewhat modified in intensity. Moreover, as I shall mention later, I am of the opinion that the chronic is really more frequent than the acute type, although the latter has been reported more frequently.

The hematologic features of acute hemolytic anemia are of considerable interest. There is usually a leukocyte count greater than 15,000 per cubic millimeter (after making allowance for nucleated red cells) with a normal distribution of the cell types and a marked shift to the left. The erythrocyte count frequently drops to a million or below, and the color index is either at unity or usually slightly higher. The stained smear shows numerous macrocytes, containing normal or slightly less than normal quantities of hemoglobin. In addition there are numerous, deeply staining microspherocytes. Nucleated red cells are frequent and may be abundant. There are some, but not a large number of, poikilocytes. Many red cells show diffuse and punctate basophilia. The number of reticulocytes is always increased and may be as large as 80 per cent or more. The platelet count is normal.

The blood picture is characteristic and when typical is practically pathognomonic of the disease. It is, of course, dependent on rapid destruction of blood, probably of large numbers of spherocytes, and, *pari passu*, rapid regenerations of blood with reflection in the blood stream of all the types of cells of a hyperplastic, regenerative bone marrow of normoblastic type.

The rapidity of the destruction of blood in the hemolytic crisis is great. In many patients the red cell count may drop a million a day and the loss of hemoglobin may be nearly as large proportionately. Even with this enormous destruction of red cells, the stained smears of the blood show all the features of intense regenerative activity of the bone marrow. No evidence of exhaustion, injury or dysfunction of the marrow has been present in patients with the acute or the chronic type of the disease. In 2 patients who died during the acute hemolytic crisis there was also no morphologic evidence of terminal exhaustion of the marrow. In a number of patients with the chronic form of acquired hemolytic icterus death was due to the profound anemia combined with hepatic insufficiency as the result of hepatic fibrosis produced by intrahepatic and extrahepatic pigment stones in the biliary system and the resultant chronic infection in the biliary ducts.

Thus the characteristic blood picture of acquired hemolytic anemia consists of profound anemia with numerous macrocytes and spherocytes, a color index at or above unity, marked reticulocytosis with other evidences of immaturity of the macrocytes, numerous normoblasts and leukocytosis. This type of morphologic alteration of the red cells was called pseudomacrocytosis by Dameshek and Schwartz, and this term aptly describes the changes in the red blood cells.

An infrequent hematologic phenomenon in acute hemolytic anemia has been the presence of an autoagglutinin or of an isoagglutinin and in some cases of an isohemolysin and/or an autohemolysin. I was not able to demonstrate autohemolysis or isohemolysis in any of my patients. An autoagglutinin and/or an isoagglutinin, however, was present in 4 patients (cases 2, 5, 8 and 12). The serum of the healthy father of one of these patients also contained an isoagglutinin for all normal types of red cells. One of these patients, early in the disease, had an autoagglutinin and an isoagglutinin for all except type O cells. Later her serum agglutinated her father's cells, which were type O. Another patient had an autoagglutinin and an isoagglutinin for all normal types of erythrocytes, but these antibodies disappeared a few hours after the spleen was removed.

The resistance of the red cells to hypotonic solutions of sodium chloride has been normal in the majority of the reported cases. In a number of instances the



fragility of the red cells has been greatly increased. Since spherocytes were present in the blood in all of my patients with this disease, although in very small numbers in 1 patient, it is not their presence alone which determines the increased fragility. Neither is the diminished resistance of the red cells dependent on the presence of autoantibodies or isoantibodies, since these antibodies are frequently not present in the serum of patients with the disease. The fragility of the red cells of most of my patients was normal. With hypotonic saline solutions the hemolysis of the red cells of 1 patient began at 0.85 per cent and was complete at 0.26 per cent. The red cells of another showed beginning hemolysis at 0.82 per cent and complete hemolysis at 0.28 per cent. The red cells of a third patient showed beginning hemolysis at 0.8 per cent and complete hemolysis at 0.26 per cent. With those of a fourth patient hemolysis began at 0.84 per cent and was complete at 0.34 per cent. This unusually wide difference in hypotonicity between beginning and complete hemolysis is seldom seen in any other disease so far as I know. Its significance will be discussed later.

Hemoglobinuria was not present in any of my patients or in the patients observed by Dameshek and Schwartz.<sup>15</sup> In regard to the more fulminating type of the disease in children, Atkinson<sup>16</sup> found that hemoglobinuria has been reported in about 30 per cent of the cases. The rarity of the presence of hemoglobinuria is probably of considerable importance in the genesis of the malady and will be discussed later.

The pathologic changes have usually been described as follows: moderate enlargement of the spleen with packing of the splenic pulp with red cells to such a degree that the normal venous sinuses have been obliterated, presence of hyaline thrombi in the radicles of the splenic vein or in the small peripheral venules, marked hyperplasia of the bone marrow, hemosiderosis of the spleen and liver and some degree of erythrophagocytosis<sup>17</sup> in both of these organs, and usually marked hyperplasia of reticuloendothelial cells in the spleen, the liver and the bone-marrow.

The marrow of 3 patients studied by Dameshek and Schwartz<sup>15</sup>

showed in each instance a very hyperplastic marrow with marked predominance of erythroblastic cells. Many of the early nucleated red cells resembled megaloblasts, but careful examination demonstrated that the resemblance was only superficial. In any event, the most mature nucleated red cells were definitely normoblastic and showed none of the megaloblastic criteria. The marrow was thus "normoblastic" and could readily be differentiated from the typically megaloblastic marrow of the liver-extract deficiency state (pernicious anemia).

#### COMMENT

I have described briefly the chief clinical and hematologic features of acquired hemolytic anemia, and an attempt will be made to correlate these with the theoretic and experimental observations which may have some importance in any consideration of the genesis of the malady.

The most striking feature of the stained blood film of the patient with the disease is the presence of large numbers of macrocytes and spherocytes. In general, from a study of the smear one gets the impression that the average

16 Atkinson, F. R. B. *Lederer's Anemia*, Brit J Child Dis 37:35, 1940.

17 Recently Hargraves, Herrell and Pearman<sup>18</sup> reported a case of erythrophagocytosis of high degree in the peripheral blood, involving monocytes, macrophages and leukocytes. The patient recovered following transfusion of blood. The clinical features resembled those of acute hemolytic anemia (acquired type), and the case was reported under the title "Erythrophagocytic Anemia (Lederer's Anemia?)" However, peripheral erythrophagocytosis has not been reported in Lederer's anemia nor in acquired hemolytic anemia.

diameter of the red cells is greater than normal in spite of the presence of numerous small deeply stained spherocytes. In addition the color index is usually at unity or even above.

The peripheral blood always shows evidences of increased regenerative demands on the bone marrow. In addition to the macrocytes there may be as many as 80 per cent reticulocytes and large numbers of normoblasts during the period of active hemolysis. Both autopsy and biopsy specimens of bone marrow have shown a hyperplastic, normoblastic marrow without other significant abnormalities. The presence of large numbers of spherocytes in the blood in this disease is of great diagnostic importance, although its significance is not yet entirely clear in spite of many dogmatic statements concerning the origin of these cells.<sup>18</sup> Haden<sup>19</sup> in a recent review of his own observations and of those of previous investigators accepted the common belief that the spherocyte is a red cell which has been injured by one of various means. According to this theory, one may assume that the life span of the spherocyte has been shortened by such an injury and that it will soon be destroyed by some means somewhere in the body. He stated that in congenital hemolytic icterus these cells are probably abnormally formed in the bone marrow although in certain other maladies they may acquire their spheroidal shape after leaving the marrow. Dameshek and Schwartz<sup>15</sup> concluded that spherocytes are formed outside of the marrow and that they represent mature red cells which have been damaged by various types of hemolytic agents. This is the prevailing belief at the present time, and most observers agree that the spherocyte is a cell of lowered resistance that was damaged after its birth and was not therefore originally an abnormally formed cell. I believe, furthermore, that the spherocyte is not necessarily of lowered osmotic resistance, although its resistance to other hemolytic agents may be diminished.

In congenital hemolytic icterus spherocytosis and increased fragility in hypotonic solutions of sodium chloride are constantly present. Neither one of these abnormalities completely disappears, although both may diminish, after splenectomy, a procedure which abolishes all other manifestations of the disease. In acute acquired hemolytic anemia spherocytosis is also constantly present, although increased fragility of the red cells in hypotonic saline solutions is only occasionally observed. Apparently in the latter disease the diminished resistance of the red cells to hypotonic solutions does not parallel the extent of the damage to the red cells by the hemolytic agent, the number of spherocytes in the circulating blood, the degree of anemia or the presence of autoantibodies in the serum. At the moment, therefore, it is not possible to explain the variable behavior of the spherocytes of acquired hemolytic anemia with hypotonic saline solutions. Both the spherocytosis and the increased fragility may be quickly abolished by splenectomy in some cases or apparently cured by transfusions of blood in other cases. In the hemolytic anemia reported as Lederer's anemia a single, small transfusion has been followed occasionally by complete cure. I was not able to find spherocytes in the blood of a patient with severe paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome), nor were Buell and Mettier<sup>20</sup>. Neither has their

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18 Hargraves, M. M., Herrell, W. E. and Pearman, P. O. Erythrophagocytic Anemia (Lederer's Anemia?) Report of a Case with Recovery, *Proc. Staff Meet., Mayo Clin.* **16** 107, 1941.

19 Haden, R. L. The Nature of Hemolytic Anemia, in *A Symposium on the Blood and Blood-Forming Organs*, Madison: University of Wisconsin Press, 1939, p. 83.

20 Buell, A., and Mettier, S. R. Paroxysmal Nocturnal Hemoglobinuria with Hemolytic Anemia (Marchiafava-Micheli Syndrome), *J. Lab. & Clin. Med.* **26** 1434, 1941.



presence been reported in cold-hemoglobinuria nor in march-hemoglobinuria.<sup>21</sup> Dameshek and Schwartz<sup>15</sup> were able to produce spherocytes by the injection of hemolytic serum or certain hemolytic agents into the blood stream. Ham and Castle<sup>22</sup> showed that when erythrosthesis was imitated *in vitro* by sterile incubation of defibrinated human blood the cells increased in volume, in spheroidicity and in osmotic fragility. Others had previously shown that in bloody spinal fluid and in hemothorax a hemolysin was produced and that the red cells gradually showed increased fragility and increased spheroidicity before disintegration occurred. Thus it is probable that the striking congestion of the spleen in acquired hemolytic anemia is in some way dependent on the alteration of the physical behavior of the red cells produced by the action of some hemolysin which damages them in the blood stream. Since these damaged red cells are probably unable to leave the spleen, for reasons not now known erythrosthesis in that organ becomes increasingly intense and this produces further alterations of these injured red cells, with increase of the rate of their dissolution by the normal action of the spleen and of the reticulo-endothelial system.

In acquired hemolytic anemia, therefore, it is probable that some hemolytic agent acting on the red cells in the peripheral circulation increases their spheroidicity and in some instances also increases their fragility as tested with hypotonic saline solutions. Since these injured cells are not destroyed at once in the blood stream, they eventually enter the spleen where they are held back for destruction. Thus the spleen becomes engorged in nearly all types of hemolytic anemia. Erythrosthesis in the spleen increases as the disease progresses, and it is probable that this factor may play an important part in the increasing tempo of hemolysis in the acute phase of the acute hemolytic crisis. Thus the red cell which has been injured but not destroyed in the peripheral vessel succumbs more or less rapidly to the normal destructive action of the spleen on effete red cells augmented by the deleterious influence of erythrosthesis in the spleen on the erythrocytes. In certain fulminating types of acute acquired hemolytic anemia hyaline thrombi have been extensive in the terminal vessels. Since they are produced by the conglutination of red cells, it is further evidence of the effect of stasis on the injured red cells in the more severe types of this disease no matter whether the stasis occurs in the spleen or in the peripheral arterioles.

This conception of the role of the spleen in the genesis of the disease seems to correlate with the facts known at the present time. However, since the cause of acquired hemolytic anemia obviously does not reside in the spleen removal of this organ will not cure the disease in every instance. In some cases the damage to the red cells by the hemolytic agent may be so great that even removing the destructive influence of the spleen and of erythrosthesis in the spleen may not be sufficient to carry the patient through the acute phase of the disease or to tide him over the critical period before the hemolytic agent either leaves the blood stream spontaneously or becomes less active in those instances in which the disease is doomed to run a chronic course.

There is another feature of acute hemolytic anemia which may be of fundamental importance in any theory of the genesis of the disease. In my cases and in those reported by Dameshek and Schwartz,<sup>15</sup> in spite of the extreme rapidity of the hemolysis, no discoloration of the urine by hemoglobin was observed. In all of the patients the icterus was of high degree. In the various types of hemoglobinuria,

21 Gilligan, D. R., and Blumgart, H. L. March Hemoglobinuria, *Medicine* 20 341, 1941.

22 Ham, H. H., and Castle, W. B. Relation of Increased Hypotonic Fragility and of Erythrosthesis to the Mechanism of Hemolysis in Certain Anemias, *Tr. A. Am. Physicians* 55 127, 1940.

on the contrary, the hemoglobinuria and the hemoglobinemia may be marked although spherocytes are absent, icterus is mild and the degree of anemia is slight in comparison with the marked hemoglobinuria

The frequency of hemoglobinuria in patients with acquired hemolytic anemia is not known accurately, although Atkinson<sup>16</sup> reported that it was present in 11 of 30 children with all types of acute hemolytic anemia. In this connection Dameshek and Schwartz<sup>15</sup> stated that when an immune hemolysin is injected into the blood stream of guinea pigs in different doses, various results are obtained. With large doses there is a fulminating anemia with hemoglobinuria, while with small doses there is a "pseudomacrocytic" anemia without hemoglobinuria. I have obtained these results by injecting rabbit serum immune to human red cells into patients with multiple sclerosis. However, I believe these experimental results oversimplify the problem. It is probable that in acquired hemolytic anemia the hemolytic agent acting on the blood cells, probably in some portion of the peripheral blood stream, is either small in amount or of low potency and that the red blood cells injured by it are consequently destroyed only in the spleen and are not hemolyzed in the general vascular system. In hemoglobinuria, on the contrary, the hemolytic agent is of small amount but of high potency, and the cells injured by it are hemolyzed largely in the blood stream before they reach the spleen and their hemoglobin is therefore set free in the blood vessels. Since the renal threshold for hemoglobin in man is about 135 mg of hemoglobin per hundred cubic centimeters of blood,<sup>23</sup> it is apparent that only small quantities of hemoglobin need to be liberated into the blood vessels to cause marked hemoglobinuria. In acquired hemolytic anemia, on the contrary, the red cells injured in the blood stream by the hemolytic agent of the disease are destroyed only in the spleen, and free hemoglobin does not enter the blood stream unless the amount of hemoglobin liberated by the hemolysis overwhelms the spleen and the liver. In hemoglobinuria the hemolytic agent destroys the red cells and liberates the hemoglobin in the blood stream, and most of it leaves the body through the kidney just as if hemoglobin had been injected into the blood vessels. In support of this hypothesis Gilligan and Blumgart<sup>21</sup> in a study of march hemoglobinuria found that even though the hemoglobinuria was of marked degree no appreciable anemia was observed in their patients, and the same general results have been observed frequently in cold-hemoglobinuria and in paroxysmal nocturnal hemoglobinuria.

One of the more interesting features of acquired hemolytic anemia occasionally reported is the presence of agglutinins or of hemolysins in the serum. Widal, Abram and Brulé<sup>5</sup> and Chauffard and Troisier<sup>6</sup> observed the phenomena associated with these and were convinced of their importance in the genesis of the disease. They assumed that the hemolysins might be endogenous or exogenous in origin. Widal and Abram<sup>8</sup> expressed the belief that the red cells in acute acquired hemolytic anemia were changed to spherocytes in the blood stream by the action of a hemolytic substance. They assumed that the malady could be explained by the theory of hemolysis developed by Bordet.

The hemolysins, according to this hypothesis, are practically completely absorbed by their specific antigen, the red cell. This combination of hemolysin and antigen will then absorb most of the complement. Thus *in vitro* the serum will be non-hemolytic, since all the hemolysin is absorbed by its antigen. The content of complement will be diminished or even absent, since it is in great part attached to the antigen-antibody union. The red cells will be completely hemolyzed if the amounts of hemolysin and complement are sufficient. If these quantities are

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23 Yuile, C. L. Hemoglobinuria, *Physiol Rev* 22 19, 1942

incomplete, the red cells will be fragile and will be hemolyzed only after the addition of more complement. In the patient with acute hemolytic anemia "the red cells are fragile to hypotonic saline solution, just as sensitized red cells are after they have been given a small dose of complement, and they will dissolve completely when placed in serum rich in complement, just as red cells sensitized to a hemolysin would." The serum *in vitro* has no hemolytic action since all the hemolysin is fixed by the red cells. Thus the serum acts as though it contained an anticomplementary substance, and it is probable that it is the unstable equilibrium acting without ceasing between the circulating hemolysin and the antihemolysin which causes the incessant variations of the state of the blood in this malady. Chauffard and Troisier<sup>6</sup> first found a hemolysin in the serum of a patient with acquired hemolytic anemia. This serum contained an autohemolysin and also an isohemolysin which disappeared when it was heated to 56 C but which returned when complement was added. They believed that the autoantibody was of fundamental importance in the disease, and they assumed, therefore, that acquired hemolytic anemia was really a hemolysinic anemia and so named the disease.

The problems concerning the relation of the autoantibodies and isoantibodies to the genesis of the disease were discussed in a recent article by Reisner and Kalkstein.<sup>24</sup> According to these authors, Wiener in a personal communication expressed his opinion that the autoantibodies were a symptom and a result of the disease rather than its cause. Apparently he expressed the belief that when massive destruction of red cells occurs, the destroyed red cells themselves under certain conditions may stimulate formation of autoantibodies. "When only a small amount of hemolysis occurs the reticulo-endothelial system can take care of the effete cells, but when large amounts of blood are destroyed the accessory mechanisms of autoantibody formation are brought into play." They stated that agglutination and hemolysis of red cells are due to the identical immune antibody acting under different conditions. "Therefore, we believe that although they may not always be found without special examination, autoagglutinins are likely to occur in most cases of autohemolytic anemia, and conversely the presence of autoagglutination in such cases may be so marked as to interfere with the satisfactory *in vitro* demonstration of auto-hemolysins." They also searched the literature and found reports of 54 instances of autoagglutination in various diseases. In many of these and in a number which I have observed no evidence of hemolysis or of hemolytic anemia was present clinically.

I was not able to demonstrate the presence of hemolysins in the serum of any of my patients. One patient (case 2) had an autoagglutinin to her own cells, type AB, and to all AB cells. Early in the disease her serum did not agglutinate her father's cells, which were type O, but later it did. The serum of another patient (case 5) agglutinated her own cells and the cells of all other normal types. Her father's serum also agglutinated all normal cell types but was not tested against his own cells. He was well and healthy and I have no explanation for the presence of an isoagglutinin in his blood. The serum of the third patient (case 8) agglutinated his own cells and all other normal type red cells, but I was unable to demonstrate any hemolysins. It is remarkable that in this instance the agglutinin disappeared in less than forty-eight hours after splenectomy. Autoagglutinins were also present in a fourth patient (case 12) of my series.

There is no convincing evidence at the present time that these antibodies are true immunologic antibodies nor are they normal human agglutinins since they

<sup>24</sup> Reisner, E. H., Jr., and Kalkstein, M. Autohemolysinic Anemia with Auto-Agglutination. Improvement After Splenectomy, *Am J M Sc* 203 313, 1942.

frequently agglutinate type O cells. They are not demonstrable in every case of acquired hemolytic anemia, and they may be present in the serum of healthy persons and in the serum of patients with a variety of diseases unassociated with any type of hemolytic anemia. One cannot dismiss them as of no importance in the genesis of acquired hemolytic anemia, yet their irregular appearance in the malady and their rapid disappearance after splenectomy in at least 1 of my patients lead me to favor the belief that their presence may be in some way determined by destruction of blood and erythrostasis in the spleen and that these antibodies are, therefore, not the causal factor in the disease nor the essential factor in the production of hemolysis. Theoretic considerations unsupported by sufficient facts are not warranted at present, and one may hope that in the future this problem may be studied more carefully as the disease is recognized more frequently.

The fragility of the red cells as tested with hypotonic saline solutions has been increased in a number of cases of acute acquired hemolytic anemia, although in the majority of instances it was normal. In 3 of my cases and in the case observed by Moschcowitz<sup>11</sup> the type of diminished resistance of the red cells was different from that I have seen in any other disease. In 1 of my cases hemolysis began at 0.85 per cent and was complete at 0.26 per cent. In another hemolysis began at 0.82 per cent and was complete at 0.28 per cent. In a third hemolysis began at 0.8 per cent and was complete at 0.26 per cent. In Moschcowitz' case hemolysis began at 0.8 per cent and was complete at 0.19 per cent.

In order to explain, if possible, the wide difference in hypotonicity between beginning and complete hemolysis one might assume that the young red cells are more resistant than normal and that the spherocytes are more fragile than normal cells. I checked the sediment in the tubes in the fragility test by smears in 1 case and found that the number of nucleated red cells was greatly increased in the more hypotonic solution. Thus it is possible that in cases of this type the circulating blood contains red cells of increased fragility, as well as cells of diminished fragility, with all intermediate degrees of osmotic resistance. However, in many cases of acquired hemolytic icterus the osmotic fragility of the red cells has been normal or but slightly increased even during a hemolytic crisis, while in other instances of the disease the striking alteration of the resistance of the red cells to hypotonic saline solutions present in 4 of my cases has not been observed. Thus it seems probable that in this disease the spherocytosis, the fragility of red cells and the degree of hemolysis are not so closely related as they are in congenital hemolytic anemia, in which increased fragility is constantly present. Furthermore, in acquired hemolytic anemia I have seen the osmotic fragility return to normal in a few days after splenectomy, while in the congenital type of the disease the increased fragility is little if at all reduced after removal of the spleen.

The theories concerning the relation of spheroidicity of the red cells and increased osmotic fragility are based chiefly on that relationship constantly present in congenital hemolytic anemia and apparently need revision if they are to apply to acquired hemolytic icterus, in which osmotic resistance may be either normal or greatly reduced. Thus in the latter disease the red cells are probably injured by a hemolysin which does not make them more fragile than normal in hypotonic saline solutions in every instance.

Widal and Abram<sup>8</sup> expressed the belief that the hemolysin in acquired hemolytic icterus is almost completely attached to the red cells. Most of the complement in the serum would therefore be absorbed by this antigen-antibody union. Thus in vitro the serum would not be hemolytic, since all of the antibody would be immediately fixed by its antigen and the complementary power of the serum would

have diminished or would be absent since all of the complement would be fixed by the antigen-antibody combination. The red cells under such conditions would be completely dissolved if the amount of complement was sufficient. However, if the quantity of complement fixed by the antigen-antibody combination was too small, the red cells would show increased fragility. Thus in the presence of red cells and hemolysin, if a quantity of complement too small to produce hemolysis is added, the resistance of the red cells would be considerably diminished.

It is remarkable that in my cases and in the reported examples of acquired hemolytic anemia the osmotic fragility of the red cells, the degree of spheroidicity and the presence of autoantibodies or isoantibodies in the serum *in vitro* do not correlate with the degree of anemia or the rapidity of its development and any satisfactory theory of the genesis of acquired hemolytic icterus must be able to explain these apparent inconsistencies.

The size of the individual or of the average red cell was not determined in my cases. In general the smears showed some changes from time to time, depending on the stage of the disease. The acute phase was usually accompanied by marked evidences of increased regenerative activity, and many red cells in the circulation were larger than normal in contrast with the microspherocytes, which were constantly present in large numbers. During the process of recovery from the disease or after a hemolytic crisis both macrocytes and spherocytes disappeared or diminished in number slowly as the blood returned to normal or to a relatively quiescent phase of the disease. I got the impression from study of smears that the average diameter of the red cells was about normal. Macrocytes and spherocytes were present in all cases, and it seemed of little importance whether one called the anemia spherocytic, macrocytic, pseudomacrocytic, or normocytic with macrocytes and spherocytes. If such a classification is to be used, and its value is doubtful, I should prefer the term "pseudomacrocytic" as used by Dameshek and Schwartz<sup>10</sup> to designate the remarkable blood picture which has been a constant feature of acquired hemolytic anemia whether of acute or chronic type.

#### PATHOGENESIS

Many of the clinical and hematologic features of acquired hemolytic anemia may be present in certain infections, in many intoxications caused by chemicals and drugs, in anemia before and after parturition and in the course of each of a number of maladies in which hemolytic crises may occur, such as sickle cell anemia, congenital hemolytic anemia and chronic hemolytic anemia of unknown cause. However, after every diagnostic possibility has been explored, there are a few cases of acquired hemolytic anemia with strikingly similar clinical symptoms and hematologic findings for which no etiologic factor can be found and which cannot be classified in any other group of cases of hemolytic anemia. In this group one may assume that the hemolytic agent is formed within the body by some unknown and probably endogenous mechanism. There is always the probability that the acquired hemolytic anemia of this group may be further divided into different types as new etiologic factors are discovered or as new types of endogenous hemolysins may be determined.

Acquired hemolytic icterus is apparently produced by the entrance into the blood stream of a hemolytic agent of unknown type and of unknown site of origin. This hemolysin may be the same autoantibody to the red cells which is often demonstrable in the serum of a patient with the disease, but at present the evidence does not support that assumption, since the autoantibody is not constantly present in the disease. However, its absence *in vitro* does not definitely exclude its possible

presence *in vivo*. I believe, as I shall discuss later, that the autoantibody is the result and not the cause of the disease.

This hemolytic agent, regardless of its nature or of its place of origin, apparently does not damage the spleen, the liver or the bone marrow since postmortem examination has failed to show any changes in these organs which cannot be explained by the presence of excessive hemolysis and profound anemia. In particular, I have not found any evidence of infection or intoxication of exogenous origin or any of the usual changes common to other known blood dyscrasias.

One may assume that the hemolytic agent damages the red cells only after they have entered the general circulation and that these damaged cells are not destroyed in the circulating blood, as they are in the various types of hemoglobinuria, although in the very acute, fulminating examples of the disease some hemoglobin may escape through the hepatolienal system to be excreted by the kidney. Thus large numbers of red cells injured by the hemolysin become spherocytes but continue to circulate in the blood stream. In some instances these damaged red cells show increased osmotic fragility but in other cases they have normal osmotic resistance. They eventually enter the spleen, where they are held back by some process not known at present. In the spleen the erythrostasis<sup>22</sup> constantly increases, and this together with the normal destructive action of the spleen, leads to increasing hemolysis of the red cells previously damaged in the circulating blood. The spleen constantly enlarges from congestion, and evidences of the destruction of blood become intense.

Since there is no evidence of damage of the spleen in the disease, one may assume that some alteration of the red cells produces a change in their physical characteristics causing them to dam up in the spleen. Certain facts are important in this respect. The Ehrlich-Morgenroth phenomenon was present in a patient observed by Dameshek and Schwartz<sup>15</sup>. Hyaline thrombi were present in the peripheral arterioles of a patient studied by Moschcowitz<sup>11</sup> and have been observed in spleens removed at operation from other patients with the disease. These hyaline thrombi are produced by local agglutination of red cells in the smaller vessels. Thus a positive Ehrlich-Morgenroth phenomenon in this disease in which hemoglobinuria is a rare occurrence is, in my opinion, not proof that hemolysis in any considerable degree is taking place in the peripheral circulation. If it were, hemoglobinuria would be a more constant symptom. It seems probable that in acquired hemolytic anemia the red cells are injured in the blood stream, that if stasis is produced agglutination takes place with considerable ease and that then a certain degree of hemolysis of the conglutinated red cells occurs *in situ*. Erythrostasis in this disease is largely limited to the spleen, although a minimal amount of stasis, leading to intravascular hemolysis and the formation of hyaline thrombi, may take place in the peripheral arterioles. I am of the opinion that the erythrostasis in the spleen, by whatever change in the physical characteristics of the red cells it may be produced, is of considerable importance in the genesis of the disease. There is also considerable clinical evidence that it may be the cause of the formation of the antibody and of the remarkable type of osmotic fragility encountered in the red cells of some patients.

The hemolytic agent in acquired hemolytic anemia apparently injures susceptible red cells constantly but with varying degrees of intensity for a period. It then may disappear spontaneously, and the patient may recover completely. Thus a patient in an acute hemolytic crisis may recover without treatment or with only one or a very few small transfusions. This outcome has been reported especially frequently in those very young patients whose records have been published as those of Ledere's anemia. The hematologic data on many of these

patients have been incomplete, but in a number the alterations of the blood have been identical with those found in acquired hemolytic anemia. Furthermore, a number of these patients have recovered only after splenectomy. In contrast to my cases, however, the number of cures in the reported cases of Lederer's anemia has been so high that I suspect either that it may be a different type of hemolytic anemia, or that, more probably, some other factor is present to explain the discrepancy. Careful study of the cases reported by Lederer and other observers has convinced me that the disease is identical with acute acquired hemolytic anemia, although it is rather remarkable that the earlier references to the latter disease were not mentioned. Since Lederer's anemia was believed to be cured in every instance by transfusions and since each author reported one or at most a few instances of the disease it is possible that those patients who died and those patients whose hemolytic anemia recurred or became chronic were not reported as having the disease described by Lederer. At least in my experience the patient with acute acquired hemolytic anemia of unknown cause and with the characteristic changes of the blood which I have described is often not cured by either transfusions or splenectomy but instead has the disease in a chronic form after an apparently acute onset. The severity and the duration of the disease certainly vary greatly. In some instances a single small transfusion will produce a cure, in others splenectomy is necessary to save the patient's life, although it may not lead to a permanent cure. One patient reported by Widal and Abiam<sup>8</sup> had a spontaneous cure after having had hemolytic crises for twelve years.

The presence of increased osmotic fragility of the red cells together with jaundice and splenomegaly in acquired hemolytic anemia has doubtless occasioned confusion of this disease with the hemolytic crises of congenital hemolytic icterus. This error may be avoided by accurate observation of the close relatives of the patient and by careful morphologic study of the blood. In my experience acute hemolytic crises of the severity seen in acute or chronic acquired hemolytic anemia are rare in congenital hemolytic icterus. Furthermore, increased osmotic fragility is constantly present in the congenital type of the disease but was observed in less than half of my patients with acquired hemolytic anemia. However, increased osmotic fragility of the red cells is not proof that the disease in question is congenital hemolytic icterus as is usually stated in textbooks and in the hematologic literature.

The ultimate outcome of the disease is extremely variable. There is a group of patients with the acute type of the disease who are cured by transfusions or by splenectomy or may even show spontaneous healing. In a large number of patients who survive the acute phase of the disease the illness thereafter runs a chronic course interrupted by hemolytic crises of variable intensity. At any stage the disease may apparently heal spontaneously or it may be improved by splenectomy. However, I have seen several patients in whom splenectomy proved to be of no value. Other patients in whom the disease takes a chronic course present jaundice, anemia and frequent hemolytic crises. Some of these die of the anemia or of intercurrent infections. Some apparently die of a combination of anemia and hepatic insufficiency with marked fibrosis of the liver. Such patients whom I have seen have pigment stones in the gallbladder, in the common duct and in the hepatic ducts and also, frequently, innumerable small putty-like pigment stones in the intrahepatic biliary ducts. Thus acquired hemolytic anemia with constant jaundice eventually becomes complicated by obstructive jaundice and by fibrosis of the liver with increased portal pressure.



## SUMMARY AND CONCLUSIONS

I have reported a series of cases of acute or chronic hemolytic anemia of the acquired type characterized by more or less rapid destruction of erythrocytes. Splenomegaly is constant, and it is probable that the destruction of blood occurs chiefly in the spleen. There is a pseudomacrocyclic blood picture, usually with a high color index. Large numbers of macrocytes and microspherocytes are present in the blood film during the hemolytic crises in the acute type of the disease or constantly in the chronic type of the disease. The red cells may show extreme osmotic fragility, or they may be normally resistant to hypotonic saline solutions. This abnormality is not related to the number of spherocytes in the circulating blood.

The blood may or may not contain autoagglutinins or autohemolysins.

The disease is neither hereditary nor congenital, and no etiologic factor has been determined in any of the reported cases.

The acute type of the disease has been reported as Lederer's anemia. Subacute and chronic types are probably more frequent than is commonly believed.

The disease may heal spontaneously, or it may be cured by transfusions or by splenectomy. The more chronic types of the disease may or may not be cured by removal of the spleen. During the serious hemolytic crisis often seen in the disease removal of the spleen may be life saving even if it does not lead to complete cure.



# THERAPEUTIC OBSERVATIONS IN CUSHING'S SYNDROME

EFFECT OF VARIOUS AGENTS ON CALCIUM, PHOSPHORUS AND NITROGEN  
EXCRETION IN A PATIENT WITH PITUITARY BASOPHILISM

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PHILADELPHIA

Skeletal decalcification has been recognized as a characteristic feature of pituitary basophilism since the syndrome was first described by Cushing, in 1932<sup>1</sup>. Such decalcification occurs likewise in those forms of Cushing's syndrome in which hyperplasia or tumor of the adrenal cortexes, rather than basophilic adenoma of the anterior lobe of the pituitary, is the dominant endocrine lesion. The demineralization of bone may be widespread but occurs chiefly in the skull, spine and pelvis. It may be so severe as to result in spontaneous or pathologic fractures, among which compression fractures of the vertebrae are common. Despite the long-recognized prominence of such skeletal demineralization, there have been comparatively few efforts to study the pathologic physiology of the process.

Freyberg and Grant<sup>2</sup> in 1936 reported detailed observations on a patient with a verified basophilic adenoma of the pituitary on whom studies of calcium, phosphorus and nitrogen metabolism were made under varying conditions of diet and medication. They reviewed the previous rather scant and inconclusive studies on calcium and phosphorus metabolism in Cushing's disease. They concluded from the study of their own case that despite the need for calcium and phosphorus these substances were not adequately absorbed. They further observed that large amounts of vitamin D, up to 200,000 U. S. P. units daily, did not facilitate the absorption of calcium and phosphorus but that calcium injected intravenously was apparently retained. They found no evidence to suggest that the parathyroids played any part in the process of demineralization and concluded that a complete understanding of the mechanism must await further study.

Bauer and Aub<sup>3</sup> reviewed the rather conflicting experimental evidence relating to the effect of the pituitary on calcium and phosphorus metabolism. They referred to a patient with Cushing's disease who was in distinctly negative calcium balance while on a low intake of calcium. After successful irradiation therapy, with subsidence of the syndrome, the degree of negativity of the calcium balance was greatly reduced. No striking abnormality in phosphorus balance was noted either before or after treatment.

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1 Cushing, H. Basophilic Adenomas, *J Nerv & Ment Dis* **76** 50 (July) 1932.

2 Freyberg, R. H., and Grant, R. L. Calcium and Phosphorus Metabolism in a Verified Case of Pituitary Basophilism, *Arch Int Med* **58** 213 (Aug) 1936.

3 Bauer, W., and Aub, J. C. Studies of Calcium and Phosphorus Metabolism. Influence of Pituitary Gland, *J Clin Investigation* **20** 295 (May) 1941.

In 1941 Albright and his associates<sup>4</sup> advanced the theory that many of the prominent features of Cushing's syndrome can be explained by assuming a hyperfunction of the adrenal cortex leading to increased gluconeogenesis from protein. This, they felt, could explain not only the diabetes but the muscular weakness, capillary fragility, cutaneous changes and osteoporosis, all of the latter being the result of a decreased supply of the protein necessary to the normal components of muscle, capillary walls, skin and the osteoid or bony matrix on which the mineral elements of bone are deposited. This theory would lead to the inference that the demineralization of bone in Cushing's syndrome is the result of an inadequate tissue framework for the deposition of calcium and phosphorus compounds rather than of an increased active withdrawal of calcium and phosphorus from the bones, such as occurs, for instance, in hyperparathyroidism. Albright and his associates included in their report the effect of estrogen, progesterone and testosterone propionate on calcium, phosphorus and nitrogen balance in their patients with Cushing's disease. One of their patients was in positive calcium balance and 1 in approximate calcium equilibrium before treatment was begun. One patient was in negative phosphorus balance and 1 in approximate phosphorus equilibrium before treatment. The administration of estrogen was followed by a temporary negative calcium balance due to increased fecal loss of calcium in at least 1 patient. Testosterone propionate produced retention of calcium with sharp reduction in urinary calcium, in 2 patients. There was likewise retention of phosphorus and nitrogen following testosterone therapy. General clinical improvement was reported to have followed the development of positive nitrogen and phosphorus balances in all of their patients.

In 1941 we encountered a patient with the classic picture of Cushing's syndrome on whom it was possible to make prolonged metabolic studies. Such studies were made at intervals from February 1941 until April 1942 with the following purposes in mind: (1) to observe the effects of varying calcium-phosphorus ratios in the diet and of various combinations of therapeutic agents on the excretion of calcium, phosphorus and nitrogen, (2) to determine the effect of such dietary and therapeutic combinations on the serum concentrations of calcium, inorganic phosphorus and protein and the activity of phosphatase in the serum, and (3) to observe the effect of such treatment on the patient's symptoms and clinical course.

The therapeutic agents employed included estrogens given orally and parenterally, testosterone propionate by intramuscular injection, calcium and large doses of calciferol (vitamin D<sub>2</sub>). These substances were administered in varying combinations.

#### REPORT OF A CASE

Miss G. S., a school teacher aged 30 years, was referred to the Hospital of the University of Pennsylvania Feb. 18, 1941, by Dr. Chalmers Montgomery, of Altoona, Pa. Her chief complaint was pain in the back of seven weeks' duration. Her past medical history had been entirely irrelevant until the age of 26. At that time (May 1937) her menses, which previously had been normal and regular since their onset, at the age of 13 years, became increasingly scant and irregular. They finally ceased altogether in May 1938. At about the same time she gained 10 pounds (4.5 Kg.), which was deposited chiefly about the face, hips and abdomen. Increasing facial hirsutism appeared, with acneform lesions on the face, neck and back. In the summer of 1937 ecchymotic areas began to appear on the legs without trauma, and these had continued to recur until the time of her admission to the hospital. Episodes of renal colic with the passage of calculi occurred, one in the autumn of 1938, one in March 1939 and one in June and July 1940. Hypertension of varying degree had been noted since June 1939. In the summer of 1940 transitory swelling, redness and burning of both legs

<sup>4</sup> Albright, F., Parson, W., and Bloomer, E. Cushing's Syndrome, Interpreted as Hyperadreno-Corticism Leading to Hypergluconeogenesis. Results of Treatment with Testosterone Propionate, *J. Clin. Endocrinol.* **1**: 375 (May) 1941.

occurred. This was followed by polydipsia and polyuria, and sugar was found in the urine in August 1940. Since that time her diet had been restricted in carbohydrate content, and she had received regular doses of insulin. She had noted progressive muscular weakness, dryness and thinning of the skin and two episodes of transitory pain and stiffness in the hips. She had been obliged to stop teaching in the summer of 1940 and had become increasingly depressed and anxious about her condition. Between October and December 1939 she received 418 roentgens (r) of irradiation to the right temporal region and 424 r to the left temporal region. Seven weeks before her first admission to the hospital she had suffered a sharp lumbar pain while attempting to open a window, and since that time she had been increasingly disabled by backache and muscular weakness, so that she was scarcely able to walk or sit erect when she entered the hospital. Physical examination showed rather pronounced

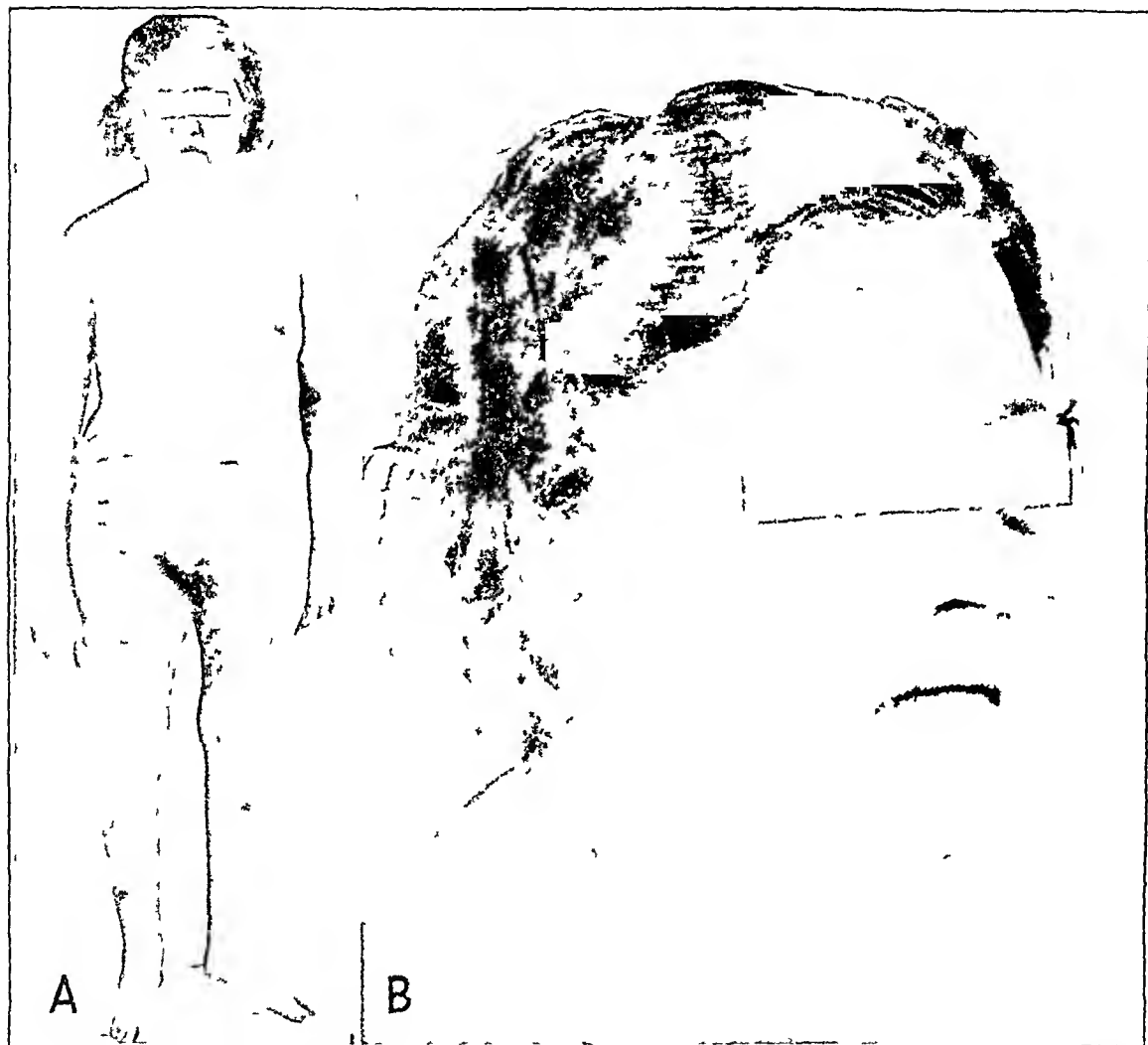


Fig 1—*A*, the patient as she appeared before treatment, *B*, the face of the patient, showing hirsutism following the prolonged use of testosterone

facial hirsuties and extensive acne, involving the face, neck and upper part of the back. The complexion was ruddy, and the skin was thin and parchment-like, with numerous purplish red striae over the thighs and the lower part of the abdomen (fig 1 *A*). Ecchymoses in varying stages of absorption were present over the legs. There was slight edema of the ankles. The patient was not obese, weighing 120 pounds (54.4 Kg) and being 5 feet 1 inch (155 cm) in height. However, relaxation of the abdominal muscles gave a false impression of abdominal obesity. The breasts were atrophic. Pelvic examination showed some vulvar irritation and a small uterus. The blood pressure varied from 180 to 190 systolic and from 110 to 115 diastolic. Further studies revealed the following: The basal metabolic rate was -18 per cent, the cholesterol content of the serum was 312 mg per hundred cubic centimeters, the inorganic phosphorus content 3.1 mg and the calcium content 10.3 mg. The fasting

blood sugar level was 107 mg per hundred cubic centimeters and the urea nitrogen content 10 mg. The serum magnesium content was 2 milliequivalents per liter. The urinary excretion of 17-keto steroids was within normal limits (13 mg in twenty-four hours). The protein content of the serum was 5.2 Gm per hundred cubic centimeters, the serum phosphatase activity, 46 Bodansky units, the carbon dioxide-combining power, 69 volumes per cent, total base, 146.9 milliequivalents per liter, and chloride, 101 milliequivalents per liter. The hemoglobin content was 17.3 Gm per hundred cubic centimeters. There were 5,660,000 red blood cells, 15,000 white blood cells and 331,000 platelets per cubic millimeter. The prothrombin time and the fragility of the red cells were normal. The volume of serum was 43.3 cc per kilogram of body weight, which is within the normal range of values for serum volume in this laboratory (normal 40 to 46 cc per kilogram). The urinalyses showed intermittent glycosuria, and the tolerance for dextrose was definitely impaired, the blood sugar reaching 315 mg per hundred cubic centimeters one hour after the first administration of dextrose (two dose method of Extton and Rose) (table 1). Roentgen examination of the skeleton showed marked demineralization involving the skull, parts of the cervical, thoracic and lumbar portions of the spine, the pelvis and the ribs. Old fractures of several ribs and of several thoracic and lumbar vertebrae and fractures of the pubic and ischial rami were noted. There was no evidence of enlargement of the sella turcica. The visual fields were full, and the ocular fundi showed only some arterial constriction. Intravenous urograms revealed functioning kidneys without evidence of deformity or of calculus formation. Examination of the adrenal areas following perinephric injection of air was first reported by the roentgenologist, Dr. E. P. Pendergrass, to show a shadow suggestive of enlargement of the right adrenal. A subsequent examination led, however, to some qualification of the original opinion, and it was finally concluded that a definite roentgen diagnosis of adrenal enlargement could

TABLE 1—Results of Dextrose Tolerance Tests

Date	Blood Sugar, Mg per 100 Cc		
	Fasting	One Half Hour	One Hour
3/6/41	130	231	315
5/23/41	70	212	246
10/24/41	79	130	190
4/8/42	116	193	218

not be made. Roentgenograms of the chest showed no evidence of substernal enlargement of the thyroid or thymus. The cardiac shadow was slightly increased in size, and the electrocardiogram showed left axis deviation. The patient, in short, presented an almost classic picture of Cushing's syndrome with the sole exception that she lacked somewhat the characteristic "buffalo type" of obesity about the shoulders and upper part of the trunk. Demineralization of the skeleton was unusually extensive and severe, and the changes in the skin were striking. Because of the questionable findings in the region of the right adrenal following perinephric injections of air and roentgen examination, it was felt that surgical exploration of the adrenals was indicated. The patient was therefore operated on by Dr. E. L. Eliason on May 28, 1941, after a period of study from March 13 to May 24 (table 2). The left adrenal was explored through a posterior incision and was found to be grossly normal. An anterior incision of the right side was then made, through which the right adrenal, the ovaries and the uterus were explored. These organs were all normal, although the right adrenal was slightly larger than the left. Biopsy sections were taken from both adrenals but showed only normal structure.

The patient was given a measured diet of known calcium, phosphorus and nitrogen content, which was maintained without variation during the various phases of study. All urine and feces were collected and separately pooled into three day lots. The limits of each three day period of collection of feces were marked by the appearance of earmine in the stool. The concentrations of calcium, inorganic phosphorus and protein in the serum were measured at intervals which varied according to the nature of the therapeutic agents employed. The methods used for the determination of protein in the serum and of calcium and inorganic phosphorus in the serum, feces and urine were identical with those referred to in a previous communication.<sup>5</sup> The nitrogen content of the diet, urine and feces was determined by the

5 Rose, E., Perloff, W. H., and Sunderman, F. W. The Effect of Low Calcium Diet and Calciferol (Vitamin D<sub>2</sub>) on Calcium and Phosphorus Metabolism. Studies on Two Parathyreoprivic Patients and One "Normal" Subject, *Am J M Sc* **202** 691 (Nov) 1941.

TABLE 2—Summary of Data on Metabolism and Therapy

Three Day Periods Beginning March 18, 1941	Therapy	Weight, Pounds	Calcium, Gm				Phosphorus, Gm				Nitrogen, Gm						
			Excretion				Excretion				Excretion						
			Intake	Urine	Feces	Total	Balance	Intake	Urine	Feces	Total	Balance	Intake	Urine	Feces	Total	Balance
I		116½	30	0.783	2.010	2.799	+0.201	2.40	0.726	0.812	1.538	-0.862	32.1	21.6	3.2	24.8	+7.3
II		116½	30	0.427	2.952	3.379	-0.370	2.40	0.600	0.951	1.551	+0.849	32.1	21.0	4.1	25.1	+7.0
III		116½	30	0.617	1.740	2.357	+0.613	2.40	0.617	1.092	1.709	+0.691	32.1	24.7	3.0	27.7	+4.4
IV			0.180	0.553	1.278	1.831	-1.351	2.40	0.670	1.191	2.161	+0.239	32.1	25.0	3.5	28.5	+3.0
V		117	0.480	0.829	0.252	1.081	-0.601	2.40	0.640	1.000	1.640	+0.760	32.1	27.6	3.3	30.9	+1.2
VI			0.180	0.747	0.350	1.097	-0.617	2.40	0.723	1.110	1.835	+0.565	32.1	29.1	4.2	33.3	-1.2
VII		115	0.480	0.660	0.375	1.035	-0.535	2.40	0.637	1.059	1.717	+0.633	32.1	28.6	4.0	32.6	-0.5
VIII	60 cc Ca Gluc IV ( 513 Gm )		2.019	1.383	0.350	1.733	+0.285	2.40	0.639	1.010	1.694	+0.736	32.1	28.9	3.9	32.8	-0.7
IX	00 cc Ca Gluc IV ( 513 Gm )	115	2.019	1.233	0.410	1.665	+0.353	2.40	0.566	1.210	1.806	+0.591	32.1	25.8	4.2	30.0	+2.1
X	1.66 mg estradiol benzoate daily I M	116½	30	0.796	2.156	2.952	+0.043	2.40	0.716	1.034	1.750	+0.620	32.1	25.2	1.7	26.9	+5.2
XI	1.66 mg estradiol benzoate daily I M	116½	30	0.719	1.845	2.564	+0.196	2.40	0.637	0.820	1.457	+0.943	32.1	21.9	2.3	24.2	+7.9
XII	1.66 mg estradiol benzoate daily I M	118½	30	0.356	2.160	2.716	+0.251	2.40	0.528	0.903	1.496	+0.904	32.1	30.7	1.9	27.8	+4.3
XIII	1.66 mg estradiol benzoate daily I M	117	30	0.415	2.928	3.373	-0.373	2.40	0.451	1.478	1.929	+0.471	32.1	17.9	2.3	20.2	+11.9
XIV	1.66 mg estradiol benzoate daily I M	115	30	0.817	3.174	3.621	-1.021	2.40	0.905	1.196	2.101	+0.299	32.1	30.7	2.0	32.7	-0.6
XV	1.66 mg estradiol benzoate daily I M	117	30	0.812	2.923	2.821	+0.176	2.40	0.731	1.102	1.833	+0.567	32.1	25.9	1.9	27.8	+4.3
XVI	25 mg testosterone propionate daily I M	117½	30	0.720	2.145	2.865	+0.135	2.40	0.726	1.235	1.961	+0.439	32.1	24.9	3.3	28.2	+3.9
XVII	25 mg testosterone propionate daily I M	118½	30	0.551	3.060	3.611	-0.611	2.40	0.456	1.122	1.608	+0.792	32.1	21.2	2.8	24.0	+8.1
XVIII	25 mg testosterone propionate daily I M	119	30	0.511	1.399	1.913	-0.913	2.40	0.386	1.351*	1.940	+0.460	32.1	19.1	2.7*	21.8	+10.3
XIX	25 mg testosterone propionate daily I M		30	0.619	2.991	3.610	-0.610	2.40	0.232	1.076	1.288	+1.112	32.1	20.1	1.9	22.0	+10.1
XX	25 mg testosterone propionate daily I M	120	30	0.472	2.293	2.767	+0.233	2.40	0.431	0.990	1.424	+0.970	32.1	15.3	2.3	17.8	+14.3
XXI	400,000 units Vitamin D <sub>2</sub>	121	30	0.395	1.890	2.485	+0.605	2.40	0.581	0.755	1.319	+1.081	32.1	21.1	1.6	23.0	+9.1
XXII	400,000 units Vitamin D <sub>2</sub>	121	30	0.345	1.870	2.215	+0.785	2.40	0.439	1.172	1.611	+0.789	32.1	22.6	3.4	26.0	+6.1
XXIII	400,000 units Vitamin D <sub>2</sub>	120½	30	0.335	1.110	1.151	+1.619	2.40	0.685	0.666	1.351	+1.049	32.1	25.3	1.9	27.2	+4.9
XXIV	400,000 units Vitamin D <sub>2</sub>	122½	30	0.347	0.960	1.107	+1.693	2.40	0.601	0.644	1.245	+1.155	32.1	22.1	2.1	24.2	+7.9
Patient out of hospital for 123 days During this time she received 1 Gm of calcium gluconate and 50,000 units of vitamin D <sub>2</sub> daily by mouth and 25 mg of testosterone propionate daily by intramuscular injection																	
Beginning Oct 13, 1941																	
I	50,000 U S P units vitamin D <sub>2</sub> daily, and 25 mg of testosterone propionate I M	118	30	0.671	1.705	2.476	+0.812	2.40	0.789	0.899	1.488	+0.912	32.1	26.1	1.5	27.6	+1.1
II	50,000 U S P units vitamin D <sub>2</sub> daily and 25 mg of testosterone propionate I M	117½	30	0.670	2.141	2.811	+0.177	2.40	0.541	0.940	1.481	+0.949	32.1	20.0	4.2	24.2	+7.83
III	50,000 U S P units vitamin D <sub>2</sub> daily and 25 mg of testosterone propionate I M	118	30	0.786	2.284	3.064	-0.076	2.40	0.489	1.060	1.489	+0.911	32.1	24.5	5.0	29.5	+3.7
Patient out of hospital 59 days During this time she received 1 Gm of calcium gluconate and 50,000 units of vitamin D <sub>2</sub> daily by mouth																	
Beginning Dec 13, 1941																	
I	50,000 units vitamin D <sub>2</sub> daily	108	30	1.060	1.918	2.924	+0.076	2.40	0.903	0.928	1.856	+0.564	32.1	30.5	1.5	35.0	-2.9
II	50,000 units vitamin D <sub>2</sub> daily	108	30	1.003	2.097	3.100	-0.100	2.40	0.912	0.908	1.820	+0.180	32.1	28.2	1.8	30.0	-0.9
III	50,000 units vitamin D <sub>2</sub> daily	107	30	0.980	1.638	2.168	+0.382	2.40	0.943	0.761	1.693	+0.705	32.1	23.8	4.2	33.0	-0.9
Patient out of hospital 67 days During this time she received 1 Gm calcium gluconate, 50,000 units vitamin D <sub>2</sub> and 1 mg stilbestrol daily by mouth																	
Beginning March 24, 1942																	
I	Stilbestrol 1 mg, Calciferol 50,000 units of vitamin D <sub>2</sub> daily	110½	30	0.610	2.420	3.060	-0.360	2.40	0.637	1.451	2.111	+0.289	32.1	22.9	1.1	27.0	+5.1
II	Stilbestrol 1 mg Calciferol 50,000 units of vitamin D <sub>2</sub> daily	110½	30	0.617	2.216	3.163	-0.163	2.40	0.776	1.372	2.108	+0.292	32.1	27.1	1.1	29.8	+2.3
III	Stilbestrol 1 mg Calciferol 50,000 units of vitamin D <sub>2</sub> daily	109	30	0.870	1.655	2.625	+0.375	2.40	0.889	1.157	2.046	+0.431	32.1	24.1	3.8	27.9	+1.2
IV	Stilbestrol 1 mg Calciferol 50,000 units of vitamin D <sub>2</sub> daily	110	30	1.042	2.398	3.440	-0.440	2.40	0.774	1.678	2.452	-0.052	32.1	24.3	4.0	29.2	+2.9

\* Calculated on 3/2 of two day specimen

† Specimen overdried

Kjeldahl method Hashed samples of the daily diet were prepared and analyzed for total calcium, phosphorus and nitrogen content The daily diet was found to contain 156 mg of calcium, 800 mg of phosphorus and 10.69 Gm of nitrogen All rejected food was weighed, and the calculated loss in calcium, phosphorus and nitrogen content was deducted from the daily intake Deficiencies in intake of calcium were compensated for, when desired, by the addition of weighed amounts of calcium lactate

Between March 13, 1941 and April 2, 1942, studies were made during four separate admissions to the hospital The significant data relating to the time and duration of the periods of study, the therapy and the dietary intake of calcium, phosphorus and nitrogen are shown in table 2 On each admission to the hospital the collections of urine and feces were not begun until at least six days after the institution of the measured diet Changes in the concentration of calcium, inorganic phosphorus and protein in the serum and the excretion of calcium, phosphorus and nitrogen in the urine and feces are shown in figures 2 and 3

The significant data in these figures may be summarized as follows

*Serum Calcium*—The calcium content of the serum remained within normal limits throughout The initial level was near the lower limit of normal (9.4 mg per hundred cubic centi-

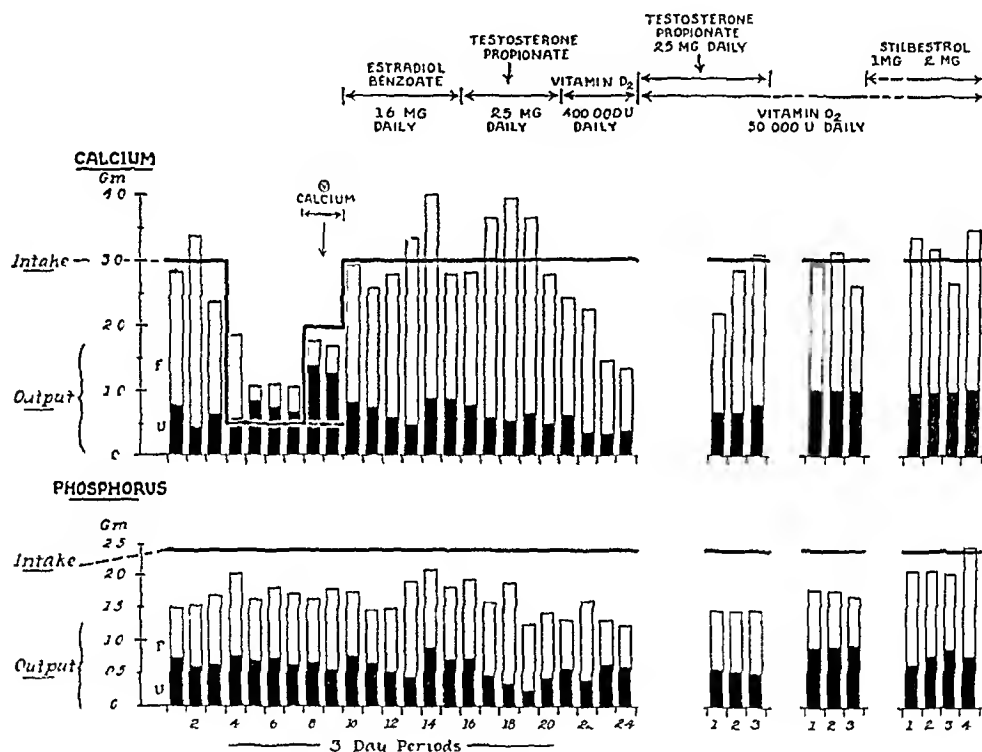


Fig 2—Data on metabolic studies

meters) Slight rises in the serum calcium were observed following the ingestion of 1 Gm of calcium per day, the intravenous injection of calcium gluconate and large oral doses of vitamin D<sub>2</sub> After the prolonged administration of calcium, vitamin D<sub>2</sub> and testosterone propionate, the calcium concentration of the serum reached its highest level, of 10.7 mg per hundred cubic centimeters It should be noted, however, that the serum protein concentration was also increased at this time

*Serum Inorganic Phosphorus*—There was a moderate rise in the level of inorganic phosphorus in the serum following the intravenous administration of calcium and a slight rise which began after the administration of testosterone propionate and continued after use of large doses of vitamin D<sub>2</sub> was begun

*Excretion of Calcium* (fig 2)—When the intake of calcium per three day period was 3 Gm and that of phosphorus was 2.4 Gm, the patient was in approximate calcium equilibrium When the intake was reduced to 0.48 Gm per three day period, a negative calcium balance developed, the output in the urine alone exceeding the intake When approximately 3 Gm of calcium, three quarters of which was administered intravenously, was given per three day period, the patient retained calcium to a moderate degree despite a sharp rise in urinary excretion of calcium The administration of large daily doses of estradiol benzoate was not accompanied with any significant change in the pattern of calcium excretion, two

phases of retention being separated by a brief interval of loss. During three of the five periods, in which large doses of testosterone were given, there was a significant loss of calcium, chiefly in the feces. During these three periods the amount of calcium lost through fecal excretion equaled or exceeded the amount ingested. The administration of large doses of vitamin D<sub>2</sub> was followed promptly by a pronounced retention of calcium, which was reflected in a decrease in both urinary and fecal excretion. After one hundred and twenty-three days of therapy with testosterone propionate, calcium gluconate and vitamin D<sub>2</sub> combined, there was retention of calcium in two of the three periods of study. No significant change occurred in calcium balance following the further administration of calcium gluconate and vitamin D<sub>2</sub> without testosterone. Following the administration of diethylstilbestrol, calcium gluconate and vitamin D<sub>2</sub> there was a negative calcium balance in three of the four periods of study.

**Excretion of Phosphorus**—The patient remained in positive phosphorus balance throughout the course of our studies except in the final period, following administration of diethylstilbestrol. There was a slight trend toward increased retention following the administration of testosterone, which was maintained during the administration of large doses of vitamin D<sub>2</sub>. Following prolonged therapy with testosterone, calcium gluconate and vitamin D<sub>2</sub>, the degree

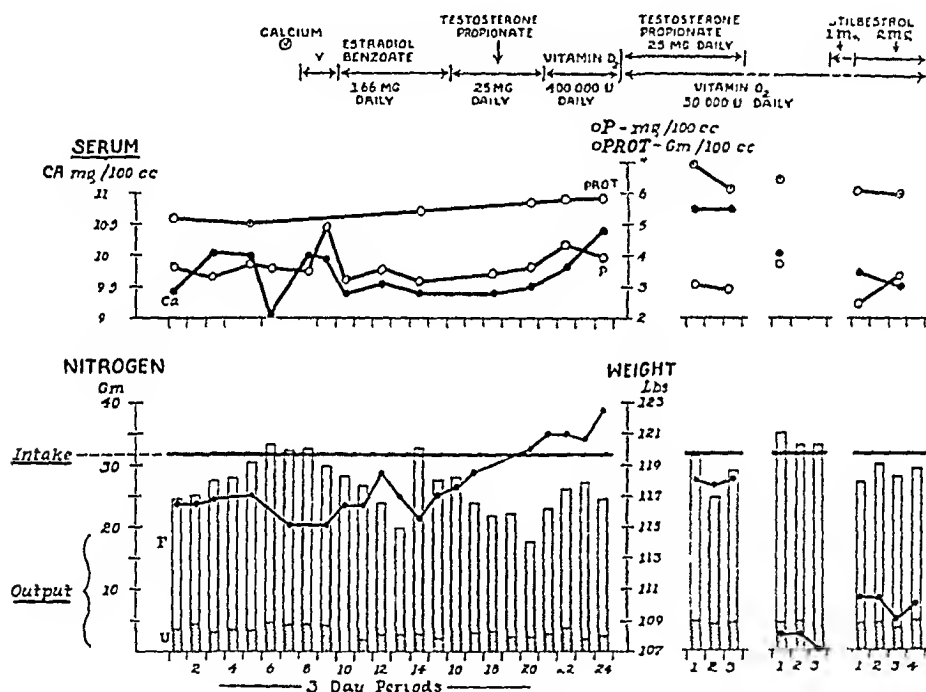


Fig 3—Data on metabolic studies

of phosphorus retention was no greater than it had been without any therapy. After the withdrawal of testosterone, however, there was a slight increase in excretion of phosphorus, which occurred chiefly in the urine. After the prolonged administration of diethylstilbestrol orally, the excretion of phosphorus reached its peak, this increase occurred in the feces.

**Excretion of Nitrogen** (Fig 3)—Fecal excretion of nitrogen varied between 2 and 4 Gm per period. The significant variations in excretion were therefore chiefly in the urine. Before therapy was begun, the patient was in positive nitrogen balance, although the degree of retention decreased progressively. The administration of estradiol benzoate was followed by a progressive increase in retention of nitrogen except for one isolated period of increased excretion toward the end of the estradiol therapy. A somewhat similar increase in retention of nitrogen followed the administration of testosterone, but this became less marked when large doses of vitamin D<sub>2</sub> were given. After prolonged therapy with testosterone, calcium gluconate and vitamin D<sub>2</sub>, there was only slight or moderate retention of nitrogen. After the withdrawal of testosterone there was consistent slight loss of nitrogen. After the administration of diethylstilbestrol, nitrogen was retained.

**Weight**—The patient's weight varied from 107 to 122 pounds (48.5 to 55.3 Kg). Minor variations occurred without obvious cause, but in general the weight tended to vary inversely with the loss of nitrogen.

Phosphatase activity in the serum increased from 4.6 to 8 Bodansky units after the completion of the first five periods of testosterone therapy and while the patient was receiving large doses of vitamin D<sub>2</sub> in May 1941. At this time, the concentration of calcium in the serum was higher than before treatment was started and nitrogen retained amounted to about 7 Gm per period. The tolerance for dextrose showed a definite improvement after the prolonged treatment with testosterone propionate, calcium gluconate and vitamin D<sub>2</sub> (see table 1, 10/24/41). The dextrose tolerance curve, however, subsequently returned toward the original level. The concentration of protein in the serum rose from a low level of 5 Gm per hundred cubic centimeters before treatment to 5.8 Gm after the first five periods of testosterone therapy and subsequently to 6.9 Gm after prolonged treatment with testosterone propionate, calcium gluconate and vitamin D<sub>2</sub>. The values thereafter remained within normal limits.

#### COMMENT

Certain striking objective and subjective changes occurred during the course of our patient's treatment. The subjective changes included a definite increase in muscular strength and improvement in the backache following the prolonged period (one hundred and twenty-three days) (see table 2) of treatment with calcium gluconate, vitamin D<sub>2</sub> and testosterone. At the same time there was noted deepening of the voice, enlargement of the clitoris and marked increase in the facial acne and hirsutism (fig. 1 B). The hirsutism decreased when use of testosterone was stopped. The objective changes noted after prolonged testosterone therapy included amelioration of the diabetes with improvement in the tolerance for dextrose (table 1, Oct. 24, 1941) and some recalcification of the spine and increase in the urinary excretion of 17-keto steroids to 25 mg per twenty-four hours.

Other definite objective changes may be listed as follows: (1) loss of calcium, chiefly through the urine, when the calcium intake was low, (2) ability to retain intravenously administered calcium, (3) retention of calcium and increased retention of phosphorus following large doses of vitamin D<sub>2</sub>, (4) retention of nitrogen during and after the first phase of testosterone therapy, whereas less marked retention of nitrogen was noted following its continued use for a period of one hundred and twenty-three days, and (5) negative calcium balance, increase in fecal phosphorus and retention of nitrogen after the administration of diethylstilbestrol.

The striking improvement in muscular power, the recalcification of the spine and the apparent amelioration of the diabetes which followed prolonged testosterone therapy, as well as the retention of nitrogen which followed the first brief phase (fifteen days) of testosterone therapy confirm the observations regarding the beneficial effect of such treatment reported by Albright and his associates.<sup>4</sup> The increase in hirsutism and acne, the deepening of the voice and the enlargement of the clitoris which also followed this treatment must not be forgotten, however.

Our observations do not agree with those of Albright and his associates in the following respects: (1) Our patient was not in negative nitrogen or calcium balance before treatment was started, and (2) the retention of nitrogen and phosphorus which followed prolonged testosterone therapy was far from striking and was, in fact, no greater than the retention of these substances noted on several occasions before use of testosterone was begun.

Our observations agree with those of Freyberg and Grant in that our patient was able to retain intravenously injected calcium. Contrary to their findings, however, our patient was able to absorb calcium and phosphorus even when the calcium-phosphorus ratio in the diet was low. Furthermore, our patient, unlike theirs, showed a marked retention of calcium and phosphorus following the administration of large doses of vitamin D<sub>2</sub>.

Adequate data pertaining to calcium, phosphorus and nitrogen metabolism have been reported in only a few cases of Cushing's syndrome. Discrepancies between



observations of various investigators cannot yet, therefore, be subjected to statistical analysis. An explanation of these discrepancies might lie in the possibility that the metabolic aberrations associated with the disease may not maintain a constant plateau of intensity. If, for example, the intensity of the basophilic pituitary or adrenal cortical dysfunction could be assumed to vary spontaneously from time to time, it might logically be inferred that variations in nitrogen, calcium and phosphorus balance would result, as well as variations in the severity of the diabetes. The ability to retain calcium, phosphorus and nitrogen as an effect of various forms of therapy might therefore vary considerably depending on the stage of the disease in which such phenomena were studied. This possibility is supported, to some extent, by the spontaneously changing trend in nitrogen excretion observed in our patient before treatment was begun (see fig 2) and by the difference in calcium, phosphorus and nitrogen balance observed in the cases of Freyberg and Grant and of Albright and his associates under similar circumstances.

The history of the passage of renal calculi by our patient on four occasions between the autumn of 1938 and the summer of 1940 suggests that during this period she may have been excreting relatively large amounts of calcium and phosphorus in the urine. Diversion of ingested calcium and phosphorus or withdrawal of these substances from her skeleton may have occurred to a greater degree during this time than when she came under our observation.

Finally, some speculation may be permissible regarding the nature of skeletal decalcification in Cushing's syndrome.

The following possible mechanisms require examination.

1 Increased withdrawal of calcium and phosphorus from the bones. This might occur as the result of (a) parathyroid hyperfunction either resulting from pituitary stimulation or secondary to a renal lesion, (b) direct action of the pituitary, as postulated by Bauer and Aub in acromegaly,<sup>3</sup> or (c) hyperthyroidism. No evidence of primary or secondary hyperparathyroidism in Cushing's syndrome is available. The possibility of some direct effect of pituitary or adrenal cortical action on the calcium and phosphorus content of the skeleton in Cushing's syndrome can neither be proved nor disproved at present. Hyperthyroidism is not a feature of Cushing's syndrome and was not present in our patient.

2 Increased urinary excretion of calcium as the result of an intrinsic renal lesion<sup>6</sup> or acidosis.<sup>7</sup> No evidence of either of these conditions has been reported to date in Cushing's syndrome.

3 Inadequate absorption of calcium and/or phosphorus resulting either from an insufficient dietary supply or a lack of vitamin D or from some defect in the mechanism of intestinal absorption. The observations of Freyberg and Grant are the only ones we have been able to find which suggest inadequate absorption of calcium and phosphorus. Our own observations certainly do not confirm this. Our patient's diet was not deficient in calcium, phosphorus or vitamin D prior to her admission to the hospital.

4 The demineralization might be similar to that described as occurring after the menopause,<sup>8</sup> since amenorrhea usually occurs early in Cushing's syndrome. The

6 Albright, F, Consolazio, W V, Coombs, F S, Sulkowitch, H W, and Talbott, J H. Metabolic Studies and Therapy in Case of Nephrocalcinosis with Rickets and Dwarfism, *Bull Johns Hopkins Hosp* **66** 7 (Jan) 1940.

7 Atchley, D N, Loeb, R F, Richards, D W, Jr, Benedict, E M, and Driscoll, M C. On Diabetic Acidosis. Detailed Study of Electrolyte Balances Following Withdrawal and Re-Establishment of Insulin Therapy, *J Clin Investigation* **12** 297 (March) 1933.

8 Albright, F, Smith, R H, and Richardson, A M. Postmenopausal Osteoporosis. Its Clinical Features, *J A M A* **116** 2465 (May 31) 1941.

history of urinary lithiasis in our patient is reminiscent of similar transitory periods of formation of renal calculi in the earlier phases of so-called menopausal osteoporosis. However, our patient failed to retain calcium consistently while receiving large doses of estradiol benzoate and was actually in negative calcium balance with an increased fecal excretion of phosphorus after the prolonged oral administration of diethylstilbestrol. Furthermore, to relate the demineralization of Cushing's syndrome to that of the menopause is simply to label it without explaining it, since the basic mechanism of so-called menopausal osteoporosis is not yet understood.

5 Inability to lay down calcium and phosphorus compounds in the skeleton because of a defect in osteoid framework or matrix. This is the explanation suggested by Albright and his associates<sup>4</sup>. It assumes a deficient supply of protein for the formation of normal matrix because of abnormal diversion of protein for gluconeogenesis. This explanation implies that the bony defect is an osteoporosis rather than an osteomalacia<sup>9</sup>. Some support for this theory is contained in the studies reported by Albright and his associates<sup>4</sup> and is likewise offered by the subjective improvement and vertebral recalcification observed in our patient following the administration of testosterone and the failure of such improvement to progress after the withdrawal of this substance.

On the other hand, the following observations noted in our case argue somewhat against this theory:

(a) Our patient was not in negative nitrogen or phosphorus balance prior to the beginning of treatment, although she was diabetic.

(b) Retention of neither nitrogen nor calcium was marked after prolonged treatment with testosterone, calcium and vitamin D<sub>2</sub>.

(c) Our patient was able to retain intravenously injected calcium without striking change in nitrogen balance. She also retained calcium after large doses of vitamin D<sub>2</sub> at a time when retention of nitrogen was declining. The fact that the serum calcium did not increase significantly during either of these phases suggests that the retained calcium may have been deposited, at least temporarily, in the bones.

If this theory is correct, one would expect to find osteoporosis in a variety of conditions when there is too little protein available for the formation of bony matrix. These would include chronic deprivation of protein, conditions associated with chronic loss of nitrogen, such as prolonged fevers and hyperthyroidism, and disorders in which prolonged hypoproteinemia exists, such as nephrosis and chronic hepatic disease. We have been able to find little evidence relating protein deprivation to osteoporosis. Malan<sup>10</sup> reported the production of atrophy of bone and osteoporosis in pigs by diets low in protein. He commented on the paucity of experimental data regarding the effect on skeletal structure of diets deficient in organic components.

Conner, Kao and Sherman<sup>11</sup> studied the effect of varying proportions of dietary protein and calcium on the body and skeletal growth and the total body calcium content of rats. They concluded that there was no consistent evidence that the increased gain in body weight which resulted from the higher levels of protein in

9 Albright, F., Bloomberg, E., and Smith, P. H. Postmenopausal Osteoporosis, *Tr. A. Am. Physicians* **55**: 298, 1940.

10 Malan, A. L. Diet and Osteomalacic Diseases in Domestic Animals, *South African M. J.* **14**: 261 (July) 1940.

11 Conner, R. T., Kao, H. C., and Sherman, H. C. Further Studies on Relationship of Plane of Protein Intake to Rate of Normal Calcification During Growth, *J. Biol. Chem.* **138**: 835 (June) 1941.

the diet had any accelerating effect on skeletal development as reflected in the percentage of body calcium Rhoads and Kasinskas<sup>12</sup> found that callus formation after experimental fracture was delayed in dogs rendered hypoproteinemic by low protein diets and plasmapheresis. However, they did not report serum calcium values for their animals. Prolonged protein deprivation in the adult as seen clinically is not associated with osteoporosis. Of the conditions associated with prolonged loss of nitrogen, hyperthyroidism and possibly acromegaly are the only ones in which osteoporosis or decalcification occurs with significant frequency, and in these diseases there may well be other factors responsible. The hypoproteinemia of chronic nephrosis does not seem to produce skeletal decalcification. It is true that hepatic disease and chronic gastrointestinal disorders have been reported in association with severe skeletal changes,<sup>13</sup> but the pathologic physiology in these conditions is so complex that protein deficiency alone can scarcely be blamed with reason.

The possibility exists that the skeletal decalcification in Cushing's disease may be associated with some chronic impairment of hepatic function, although symptoms of disease of the liver are not characteristic of the syndrome. Studies of hepatic function in pituitary basophilism have not been reported. Although the protein level of the serum was low in our patient at times, a recent test of her hepatic function by the bromsulphalein method was normal.

It seems reasonable to conclude that the theory of protein deficiency as the basis of the osteoporosis of Cushing's disease still lacks proof, although some evidence in its favor exists.

#### SUMMARY

The case of a 30 year old woman with pituitary basophilism in whom skeletal changes were particularly striking and in whom the diagnosis was reached by exclusion is reported. Studies of the concentration of calcium, phosphorus, protein and phosphatase in the serum, the dextrose tolerance and the excretion of calcium, phosphorus and nitrogen before and after the use of various therapeutic agents and with diets of varying calcium content are reported. The therapeutic agents employed included estriadiol benzoate, testosterone propionate, vitamin D<sub>2</sub>, calcium gluconate and lactate and diethylstilbestrol, in varying combinations. Subjective and objective responses to treatment are described, and our observations are compared with those in similar studies reported by others. The possibility is mentioned that spontaneous variations in the intensity of the various metabolic aberrations in Cushing's syndrome may explain some of the discrepancies in the studies reported to date. Several possible explanations of the skeletal decalcification characteristic of the syndrome are briefly considered. It is concluded that no completely satisfactory explanation of the skeletal demineralization in Cushing's disease is yet available.

#### ADDENDUM

Further irradiation therapy was given to the pituitary and parathyroid areas in our patient between April 1 and 16, 1942. The patient has recently returned for further observation, which was carried out in the hospital from Aug 6 to Aug 15, 1942. Between April 22, 1942 and this admission the patient had received 25 mg of testosterone propionate twice weekly by intramuscular injection and had also taken by mouth 2 mg of diethylstilbestrol, 4 Gm of

12 Rhoads, J. E., and Kasinskas, W. The Influence of Hypoproteinemia on the Formation of Callus in Experimental Fracture, *Surgery* **11** 38 (Jan) 1942.

13 Ask-Upmark, E. Osteomalacia hepatica, *Acta med Scandinav* **99** 204, 1939. Mentha, C. Osteodystrophies pancreatiques humaines et experimentales, *Schweiz Ztschr f allg Path u Bakt* **4** 209, 1941. Siskl, H. Osteomalacie bei langdauernder Erkrankung der Gallenwege, *Frankfurt Ztschr f Path* **55** 120, 1941.

calcium gluconate and 100,000 U S P units of vitamin D<sub>2</sub> daily. Ten units of protamine zinc insulin and 10 units of unmodified insulin had been injected daily. Her diet had been unrestricted.

She still complained of weakness of the back and a burning lumbar backache after prolonged standing but was able to walk six to eight blocks without fatigue. Scant menstrual bleeding had occurred from July 22 to July 29 for the first time in four years. Physical examination showed no changes except that the facial acne and hirsutism had decreased. Roentgen examination of the thoracic and lumbar portions of the spine showed evidence of healing of the vertebral fractures, but marked demineralization of the skull and spine was still noted and had not improved since the examination made in April 1942. Estimations of the serum protein, phosphatase, calcium and phosphorus yielded values within the normal range. Serum cholesterol was found for the first time to be within the normal range (189 mg per hundred cubic centimeters). A test of dextrose tolerance by the one hour, two dose method of Exton and Rose gave the following values: fasting blood sugar, 110 mg per hundred cubic centimeters, one-half hour blood sugar, 146, and one hour blood sugar, 150. Urine collected during the test period contained no sugar. It is thus evident that some general improvement had occurred.

The testosterone propionate was supplied by the Schering Corporation. Part of the calciferol was supplied by the Winthrop Chemical Company.

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# COLD HEMAGGLUTINATION WITH SYMMETRIC GANGRENE OF THE TIPS OF THE EXTREMITIES

REPORT OF A CASE

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The antigen-antibody reaction between human erythrocytes and serum in which hemagglutination is observed only at low temperatures (below 20 C ) has attracted the attention of immunologists<sup>1</sup> and clinicians<sup>2</sup> for many years. Unusual serologic features of this reaction, its association with so many diverse pathologic states (Raynaud's syndrome, acute and chronic acquired hemolytic anemias, trypanosomiasis, acute bacterial infections, cirrhosis of the liver, leukemia, pernicious anemia, lymphoblastomas and bland venous thrombosis<sup>2a</sup>) and its presence in low titer in at least 95 per cent of normal persons<sup>3</sup> have been recorded. There is only 1 report<sup>4</sup> of the occurrence of gangrene of the extremities due to the action of a cold hemagglutinin. In the case we are reporting gangrene was much more extensive.

In the data that follow the essential characteristics of the phenomenon are presented. The differences between cold hemagglutination, panagglutination and pseudoagglutination (rouleau formation) will not be discussed. Wiener<sup>5</sup> and Levine<sup>6</sup> have written exhaustively on this subject. The term autoagglutination will not be used, since it refers only to the agglutination of erythrocytes by

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Dr Stats was a Littauer Fellow in Pneumonia Research, Harlem Hospital. Dr Bullowa is clinical professor of medicine, New York University College of Medicine, and visiting physician, Harlem Hospital and Willard Parker Hospital.

From the Medical Service of Harlem Hospital, City of New York Department of Hospitals, Dr Oswald La Rotonda, director, and the Littauer Pneumonia Research Fund of New York University College of Medicine, Dr Jesse G M Bullowa in charge.

1 Landsteiner, K. Ueber Beziehungen zwischen dem Blutserum und den Korperzellen, *Munchen med Wchnschr* **50** 1812, 1903.

2 Klein, A. Ueber die Untersuchung der Formelemente des Blutes und ihre Bedeutung fur die praktische Medizin, *Wien klin Wchnschr* **40** 1569, 1890.

2a Since this article was presented, two publications have appeared concerning the presence of cold hemagglutinins in atypical (virus?) pneumonia. They are as follows: Peterson, O L, Ham, T H, and Finland, M. Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias, *Science* **97** 167, 1943. Horstmann, D H, and Tatlock, H. Cold Agglutinins. A Diagnostic Aid in Certain Types of Primary Pneumonia, *J A M A* **122** 369 (June 5) 1943.

3 Kettel, K. Studien uber die Frage der Kalteagglutination des Blutes bei Menschen, Vorlaufige Mitteilung, *Acta path et microbiol Scandinav* **5** 306, 1928.

4 McCombs, R P, and McElroy, J S. Reversible Autohemagglutination with Peripheral Vascular Symptoms, *Arch Int Med* **59** 107 (Jan) 1937.

5 Wiener, A S. Blood Groups and Blood Transfusion, ed 3, Springfield, Ill, Charles C Thomas, Publisher, 1943.

6 Levine, P. On Pseudo-Agglutination and Cold Agglutination, *Ukrain Ztschr f Blutgruppenforsch* **2** 17, 1928.

homologous serum It does not necessarily imply the all-important factor of cold Cold hemagglutinins agglutinate homologous erythrocytes but in addition agglutinate all human and many animal erythrocytes

#### REPORT OF CASE

The patient was a 64 year old American Negro who had lived in Virginia until his forty-fifth year, working in tobacco warehouses He then moved to New York city For the next five years he worked in an aluminum refinery Here he was exposed to intense heat in close proximity to molten aluminum On several occasions he sustained minor burns of the skin when the metal splashed Toward the termination of this employment he noted the beginning of the disease which brought him under our observation fifteen years later

He had had a penile sore in his youth but had never received antisyphilitic treatment He was married at the age of 20 His wife had six pregnancies, all of which terminated in living children, none of whom have shown clinical or serologic evidence of syphilis

Except for the present illness he had been remarkably well Fifteen years before admission he noticed tingling, burning and numbness of the tips of his fingers and of his toes on exposure to a low environmental temperature These symptoms invariably followed even a ten to fifteen minute exposure to the winter temperatures in New York The symptoms started while the patient was in the cold, they rapidly subsided when he entered a warm room Often he experienced sharp pain in the epigastrium accompanying the painful sensations in the extremities This was also short lived, clearing up rapidly when the environmental temperature was raised The first urine passed after any such episode was extremely dark, resembling coffee There was no dysuria, however Thereafter the urine looked normal to the patient These attacks of pain in the abdomen and extremities and the dark urine occurred only and always after exposure to cold and except for transient distress did not inconvenience the patient He looked on them as a "peculiar" reaction Tingling or pain on exposure to cold was never experienced in the tip of the nose or lobes of the ears He had never observed any tingling of the tongue or other uncomfortable sensations in his mouth or pharynx after the ingestion of cold drinks or ice cream He had never experienced cyanosis or pallor of his digits, nor had he ever noted urticarial or other cutaneous reactions to cold

Two weeks prior to admission to the Harlem Hospital, the patient was exposed to a dry early morning temperature of approximately 5 F for about sixty minutes while waiting for a bus During this time he was clad warmly and wore kid gloves and shoes and cotton socks He was not able to exercise much during his long wait and spent most of the hour standing still He observed the same tingling of his fingers and toes that he had experienced many times before, and the first urine passed was dark On this occasion, however, though the urine shortly resumed its normal appearance, the tingling and the pain continued These symptoms persisted with moderate severity, unrelieved by environmental warmth Despite this discomfort he did not remain in bed but continued to be up and about indoors until the pain became so severe that he sought hospital care

On his admission to the service of Dr Oswald La Rotonda, on Jan 17, 1942, he presented an unusual diagnostic problem The general physical examination revealed an acutely ill, slightly obese, intelligent, darkly pigmented Negro The rectal temperature was 102 F Examination of the head and neck gave no significant results Examination of the fundi revealed slight widening and irregularity of the arterial light reflex The heart was of normal size There were no abnormal sounds The heart rate was regular, 90 beats per minute The blood pressure was 160 systolic and 90 diastolic The lungs were clear The abdomen was obese The viscera were not palpable, nor were there palpable masses The results of neurologic examination were negative In the upper extremities the arterial pulses were easily felt, from the subclavian to the digital The axillary, radial, ulnar and digital arterial pulses had a bounding quality Slight thickening of the radial arteries was evident on palpation The tips of all the fingers to the distal interphalangeal joints were tense, tender, painful and cool to the touch In the lower extremities all the arterial pulses were easily felt These included the iliac, femoral, popliteal, anterior and posterior tibial and dorsal of the foot (the last three after subsidence of the edema) There were pitting tender edema and inflammatory warmth of each leg in the lower half anteriorly and the lower two thirds posteriorly Both feet were moderately edematous and tender The patient could not move his toes, and they were insensitive to pain stimuli The toes were exquisitely tender and cool to the touch

Detailed laboratory study gave the following results

1 The specific gravity of the urine was 1.026 and the color amber, the urine was clear, and tests for albumin and sugar gave negative results, microscopic examination showed a rare white blood cell, the result of a benzidine test for occult blood was negative

2 The Kahn test of the blood for syphilis gave negative results

3 The roentgenologic examination of the chest revealed slight enlargement of the left ventricle, the lungs were normal

4 The electrocardiogram revealed a depressed  $T_1$  and a flat  $T_2$  wave and left ventricular preponderance, changes indicative of myocardial disease

5 Studies of the hepatic function revealed that the icterus index (acetone) was 30, the blood content of cholesterol, 180 mg, and of cholesterol esters, 90 mg per hundred cubic centimeters, the reaction to the cephalin flocculation and the Takata-Ara test, negative,



Fig 1—Dry gangrene of the tips of the fingers

the reaction to the galactose tolerance test, 2 Gm excreted in four hours, and to the bromsulphalein excretion test (5 mg per kilogram), less than 5 per cent dye retention in one-half hour, the blood content of albumin, 4.5 Gm, and of globulin, 2.5 Gm per hundred cubic centimeters, and the serum formaldehyde-gel reaction, negative

6 A test of renal function revealed a maximal specific gravity of the urine of 1.028, other determinations were not deemed necessary

7 Roentgenologic examination of the gastrointestinal tract with special reference to the small intestine revealed hypermotility, puddling of barium sulfate, a segmental arrangement and loss of normal jejunal and ileal markings, when this procedure was repeated after three weeks of intensive treatment with thiamine hydrochloride (525 mg given subcutaneously) the changes were less marked

8 Roentgenologic examination of the arms, forearms, thighs and legs did not reveal any calcification of vessels

When the patient was admitted a definite diagnosis was not made and the following tentative diagnoses were entertained impending gangrene, thrombophlebitis or thromboangitis obliterans and paroxysmal hemoglobinuria

During the first week the patient was treated for thrombophlebitis, he continued to complain of pain in his toes and to a lesser degree in his fingers. His temperature remained between 101 and 102 F. The edema and pain in the legs gradually subsided. At the end of this period, despite his intense pigmentation, it became obvious that gangrene of all the toes and of the tips of seven fingers was taking place. In an attempt to delay or forestall some of these changes, he was treated with heparin and 3,3'-methylenebis-(4-hydroxycoumarin) for three weeks. No beneficial effect could be observed as a result of this medication.

At this time, one week after the patient's admission to the hospital, a chance observation provided the lead to the diagnosis. During the course of a hematologic study (of blood from the ear), almost complete agglutination of the red cells was visible grossly as soon as dilution in a counting pipet was carried out. After several efforts, a successful dilution was

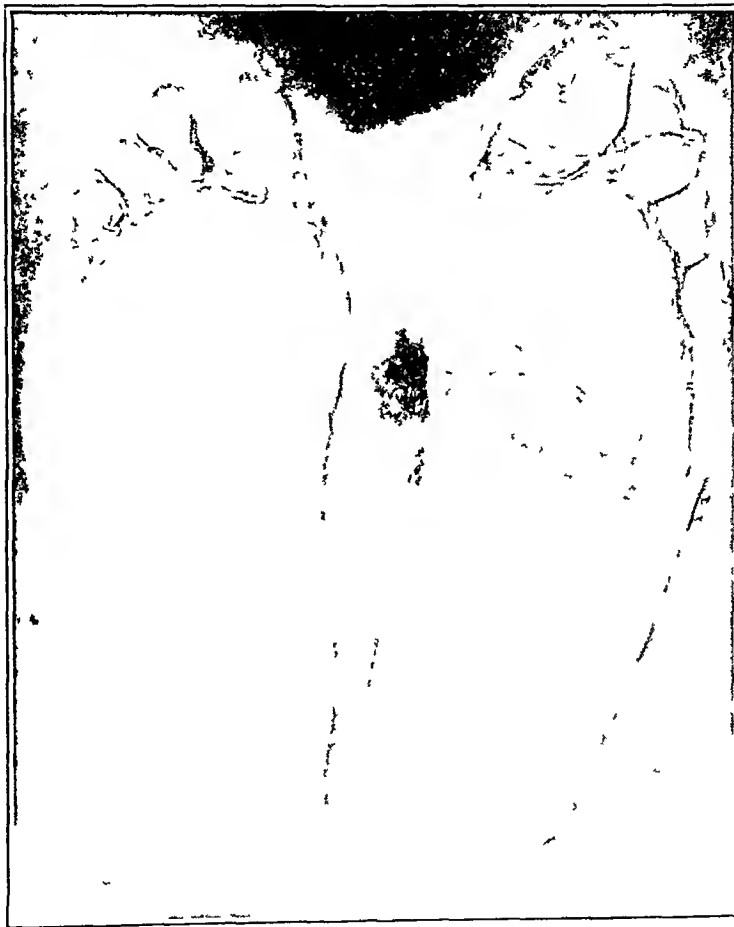


Fig 2—Dry gangrene of the toes

made with warm isotonic solution of sodium citrate, but when an attempt was made to perform the count several minutes later, clumping had again occurred. When this pipet with its contained cells and fluid was heated gently, complete dispersion of the cell clumps occurred.

The patient remained in bed for two months. During this time the temperature fell to normal and the progressive changes of dry gangrene of the digits developed.

The gangrene occupied all of the toes as far as the metatarsophalangeal joints. The fingers were much less severely involved. On the left hand the tips of the terminal phalanges of the second, third, fourth and fifth fingers were involved, whereas on the right both the first and second fingers were spared. This difference in degree was also demonstrated by roentgenographic means. Roentgenograms of the feet revealed several large, sharp, moth-eaten foci of bone destruction without any reaction in the proximal parts of the distal phalanges. There was no calcification in the blood vessels of the feet.

The pain gradually disappeared as the acute inflammatory element of the initial stages subsided. It could then be observed that the line of demarcation between the gangrene and



the normal skin was exceedingly sharp. During the next four months the patient was up in a wheel chair. Therapy to the lesions consisted of daily bathing of the feet in diluted solution of sodium hypochlorite U S P and application of hydrous wool fat to the skin. Thymol iodide powder was dusted on the toes. The toes and the gangrenous foci of the fingers became sclerotic and mummified. Occasionally small purulent foci formed, but these drained spontaneously. Examination eleven months after the onset showed that all the gangrenous areas had sloughed and the stumps of the digits were healing. Figures 1 and 2 show the condition of the hands and feet two months after the onset of the gangrene.

The finding of hemagglutination in the red cell counting pipet provided the impetus for a detailed study of the characteristics of the phenomenon. Additional aspects of the problem will be presented in other communications.

#### EXPERIMENTAL STUDIES

1 *Characteristics of Cold Hemagglutination*—The following experiments were performed

(a) Venous blood was collected in a tube containing 3.8 per cent solution of sodium citrate and in a dry tube. The latter tube was placed at 37 C and the blood allowed to clot firmly. The expressed clear serum was removed. The former tube was centrifuged, the plasma was removed and replaced with five volumes of 0.85 per cent sodium chloride solution. The mixture was warmed to 37 C in a water bath and then centrifuged. This procedure of washing with warm saline solution and discarding the supernatant clear saline solution after centrifugation was performed six times. When red blood cells prepared in this manner were mixed with 0.85 per cent sodium chloride solution or normal human serum of the same blood group and kept at 4 or at 37 C for one hour, they remained evenly dispersed (except for slight sedimentation) and agglutination did not occur. When the patient's serum, prepared as before, was mixed with either homologous or heterologous red blood cells and the mixture placed at 4 and at 37 C for one hour, the most intense agglutination was observed in all instances at 4 C but none at 37 C (except low titer isoagglutination with red cells of other blood groups).

These experiments show that the agglutinating effect resided in the patient's serum and not in his red cells and that heterologous as well as homologous erythrocytes were agglutinated by it. The patient's red blood cells were not affected by heterologous human serum.

In all subsequent experiments the cells and serum of the patient were prepared in the manner described.

(b) A titration for agglutination at 4 C was carried out. The erythrocytes were used in 2 per cent suspension. Mixtures of 0.1 cc of a suspension of homologous red blood cells and 0.4 cc of progressive geometric dilutions of the patient's serum were kept at 4 C for sixteen hours, and agglutination was determined by gross and microscopic observation. This test was performed on many occasions, and fluctuation in titer was observed from 1:3,000 to 1:32,000, i. e., it was possible to show agglutination in the cold with a specimen of the patient's serum diluted 1:32,000 with 0.85 per cent sodium chloride solution. Retesting eleven months after the onset of the gangrene revealed the same titer of the serum. A serum with such extraordinary powers of cold agglutination has rarely been recorded. High titers of cold hemagglutination have been reported.<sup>7</sup> Cold hemagglutinins could not be demonstrated in the spinal fluid.<sup>8</sup>

(c) An understanding of the rapidity and the completeness of the cold agglutination reaction is essential to interpretation of the clinical observations in the present case. In an experiment to reveal these, 1 cc of washed packed homologous red blood cells was mixed at room temperature with 1 cc of the patient's serum. At this temperature the cells were slightly agglutinated. When the temperature was lowered to 4 C by immersion of the tube in ice water, agglutination was grossly visible in less than one minute. In two minutes the

7 Wheeler, K. M., Gallagher, H. J., and Stuart, C. A. An Unusual Case of Autoagglutination, *J. Lab. & Clin. Med.* **24** 1135, 1939. Jessen, C. U., and Bing, J. Methods for Differentiating the Cause of Increased Sedimentation Rate, *Acta med. Scandinav.* **105** 287, 1940.

8 Riebeling, C. Ueber einen Fall von sog. Paragglutination, *Med. Klin.* **29** 1440, 1933.

cells were tightly agglutinated. The mass of agglutinated cells had the appearance of a gel. When the temperature was changed to 37 C by immersion in a constant temperature water bath, breaking up of the massive agglutination was apparent in thirty seconds, and in two minutes complete dispersion of the red blood cells had occurred. If the temperature was suddenly lowered to 4 C the same rapid agglutination occurred. This process could be repeated many times without apparent cellular injury or change in the phenomenon.

(d) Experiments were performed to show more clearly the relationship of agglutination to temperature. Geometric dilutions of the patient's serum were incubated for one hour with the patient's red blood cells, as in experiment *b*, at various temperatures and agglutination recorded. The results of this experiment are shown in the following tabulation.

Temperature (C)	Agglutination Titer
0	+ 1 3,200
4	± 1 3,200
6	+ 1 1,600
13	+ 1 800
20	± 1 50
28	Negative

(c) An experiment to demonstrate the action of the antibody *in vivo* was carried out. Iwai and Meisai<sup>9</sup> described visible agglutination of the red blood cells in the conjunctival capillaries of 2 patients with Raynaud's syndrome and a high titer (1 500 to 1 1,000) of cold hemagglutination. Other studies have demonstrated erythrocyte agglutination in postmortem tissue sections.<sup>10</sup>

The venules and capillaries of the bulbar and palpebral conjunctivas in each eye were visualized under the slit lamp binocular corneal microscope and were seen to be normal. The conjunctival sacs were irrigated with 100 cc of iced isotonic solution of sodium chloride for one and one-half minutes and the vessels immediately observed. A picture was seen similar to that of the retinal vessels in the early postagonal state. Marked segmentation of the blood columns—apparently by clumps of erythrocytes—was readily seen. Between neighboring clumps one could see what appeared to be clear plasma. The segments and clumps were moving slowly. As observation was continued and the eye exposed to a normal environmental temperature (24 C), the segmentation slowly disappeared. This procedure was carried out several times in each eye without complications. The distress of the intense cold was soon dissipated. Irrigation of the conjunctival sacs of a normal person in this manner gave rise to an immediate blanching, followed by a reactive hyperemia.<sup>11</sup> Figure 3 demonstrates the effect of cold on the conjunctival vessels of the patient's eye.

**2 Hemoglobinuria**—The reliable history of the repeated passage of coffee-colored urine after exposure to cold and the absence of hemoglobin in routine urinalyses made study of this point important. It had been shown by other investigators that in syphilitic cold hemoglobinuria (presence of a cold hemolysin and a positive Donath-Landsteiner reaction<sup>12</sup>) immersion of an extremity in cold water was often followed by a paroxysm of hemoglobinuria (Rosenbach<sup>13</sup>). The following experiment was carried out in an attempt to demonstrate hemolysis *in vivo* in the present instance.

The syringes were adequately rinsed in 0.85 per cent sodium chloride solution, and 9 cc of venous blood was drawn carefully without undue stasis from each arm into 1 cc of freshly prepared 3.8 per cent sodium citrate solution. The blood and the anticoagulant were gently mixed. The right forearm was then immersed in a basin of cracked ice and water (temperature 4 C) for twenty-five minutes and the left arm kept at room temperature (20 C). After ten minutes had elapsed venous blood, as before, was drawn from the left arm. At the end of twenty-five minutes the right arm was removed from the water and dried, and

9 Iwai, S, and Meisai, N. Etiology of Raynaud's Disease, Japan M. World **6** 345, 1926.

10 Lewin, O. Zur Frage der Zulassigkeit der Bluttransfusion bei bestehender Panagglutination, Wien klin. Wchnschr. **47** 714, 1934.

11 Irrigation was performed with the assistance of Dr. Arthur Minsky, associate ophthalmologist, Harlem Hospital.

12 Hemolysis after warming of chilled blood.

13 Rosenbach, cited by MacKenzie, G. M. Paroxysmal Hemoglobinuria. Review, Medicine **8** 159, 1929.

then venous blood was drawn from each arm. Both arms remained at room temperature. At appropriate intervals for one and a half hours blood was drawn from the two arms simultaneously. All samples were then centrifuged and the supernatant plasma removed. The various specimens of plasma obtained were tested for hemoglobin by a quantitative technic which was a modification of the benzidine method of Bing and Baker<sup>14</sup>. Urine was obtained before and after the experiment and tested for the presence of hemoglobin. Two samples of the plasma from the arm which had been in the cold were analyzed in the Hardy recording spectrophotometer<sup>15</sup> for determination of the nature of the pigments present. The results of these studies are shown in figures 4 and 5.

Hemolysis occurred only in the cold extremity, showing that it was a local phenomenon. The pigment liberated to the plasma was oxyhemoglobin, indicating that chemical change



Fig 3—Bulbar conjunctiva immediately after irrigation of the conjunctival sac with cold saline solution. Below are the cornea and iris. Note the blood vessels and the segmental interruption of the blood column in the left third of the vessel running transversely ( $\times 25$ ).

did not occur, for this is the normal pigment of the red blood cells. Note should be taken of the rapidity with which the hemoglobin disappeared from the plasma. The lack of hemoglobinemia in the warm arm and the absence of hemoglobinuria may be explained by several factors. The cold undoubtedly caused marked reduction in the blood flow in the exposed arm, the free hemoglobin was rapidly diluted with the plasma of the remainder of the body, the mechanisms which existed for the removal of plasma hemoglobin rapidly removed this

14 Bing, F. C., and Baker, R. W. Purification of Benzidine, and an Improved Reagent for Estimating Hemoglobin, *J Biol Chem* **95** 387, 1932.

15 The analysis was performed at the Electrical Testing Laboratories, Inc., New York.

pigment There were no untoward symptoms in the patient as a result of this or similar experiments There was no systemic or local reaction Undue hemolysis *intra vitam* was not observed in other experiments as a consequence of prolonged venous stasis

3 *Syphilis*—The exclusion or inclusion of syphilis as a contributing factor was deemed essential because of the history that a chancre had probably once been present, that coffee-colored urine had been passed after exposure to cold and that an antibody acting in the cold against homologous red blood cells was present

a The reactions to serologic tests<sup>16</sup> were as follows diagnostic Kahn test of the blood, negative heavy, Kahn exclusion test of the blood,  $\pm$ , Wassermann test of the blood, negative, Mazzini test of the blood, 2 plus, Kahn verification test of the blood, negative type, Wassermann test of the spinal fluid, negative, Kahn test of the spinal fluid, negative, and colloidal gold curve test of the spinal fluid, 0000000000

b The Donath-Landsteiner test<sup>12</sup> was performed many times with varying serologic techniques The erythrocytes were used in concentrations of 30, 20, 10 and 5 per cent packed volume The patient's serum was used fresh or inactivated (by heat) with the addition of an excess of active guinea pig complement The period for cold incubation varied from ten minutes to one hour In none of these tests was a positive result obtained All tubes containing the patient's serum and cells showed agglutination in the cold

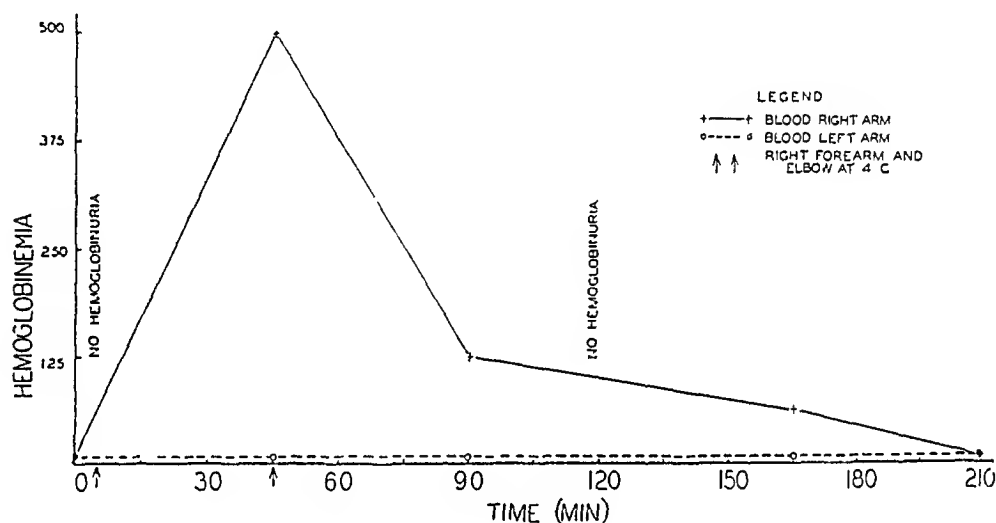


Fig. 4—The relationship between hemoglobinemia and the time after exposure of the forearm to cold The hemoglobinemia is expressed in milligrams of hemoglobin per hundred cubic centimeters of plasma

We conclude from these serologic tests and from the absence of clinical evidence of syphilis that the patient had no evidence of active syphilitic infection

4 *Hematologic Status*—The rare occurrence of cold hemagglutination associated with hemolytic anemia, the history of passage of coffee-colored urine and the occurrence of hemoglobinemia on exposure to cold made the determination of the status of the blood important

Studies of the blood showed the following picture

- Hemoglobin, 84 per cent (14.5 Gm per hundred cubic centimeters = 100 per cent)
- Red cells, could not be counted accurately
- White cells, 12,000 per cubic millimeter
- Platelets, could not be counted accurately
- Segmented neutrophils, 56 per cent
- Nonsegmented neutrophils, 4 per cent
- Lymphocytes, 31 per cent

16 The Kahn tests were performed by Dr. Reuben Kahn, Ann Arbor, Mich.

Monocytes, 6 per cent

Segmented eosinophils, 3 per cent

Reticulocytes, 1.5 per cent

Hematocrit reading, 39.1 per cent

Hypotonic fragility of red cells no hemolysis, 0.72 to 0.48 per cent sodium chloride solution, partial hemolysis, 0.44 to 0.36 per cent sodium chloride solution, complete hemolysis, 0.32 per cent sodium chloride solution

Price-Jones curve diameters of red cells (500), 7.30 microns, curve of all diameters, normal

Quantitative test of urobilinogen excretion (Watson's method<sup>17</sup>) stool (four days), 70.2 mg per day, urine (two days), 0.8 mg per day

Bleeding time (Duke's method), three minutes

Coagulation time (Lee and White method), eleven minutes

Clot retraction, present in four hours

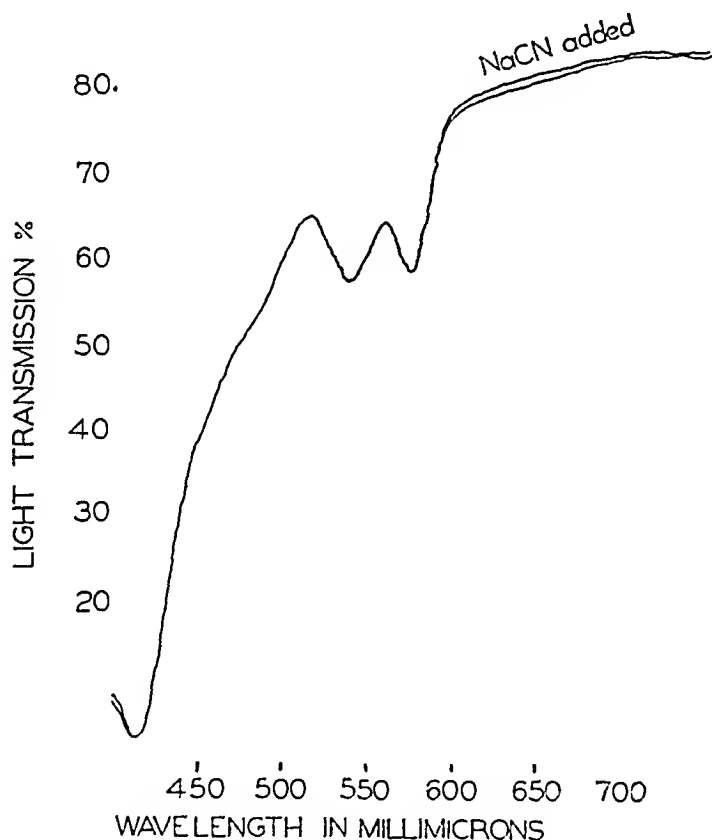


Fig 5—Spectrophotometric analysis of the hemoglobin pigment liberated, as shown in figure 4

Sedimentation rate (Wintrobe's method) one hour—at 1 C, 4.5 mm, at 9 C, 22.0 mm, at 19 C, 29.0 mm, at 24 C, 15.5 mm, at 37 C, 48.5 mm

Plasma prothrombin index (Quick's method), 100 per cent

Blood group O, Rh factor absent, MN type, anti-Rh antibody absent

Serum isoagglutinin titer anti-A, 1/128, anti-B, 1/32

Hemolysis test with acidified serum (used by Ham<sup>18</sup> in cases of paroxysmal nocturnal hemoglobinuria), negative result

From these figures we conclude that there was no significant abnormality in the peripheral blood and that the rate of destruction of erythrocytes was normal

<sup>17</sup> Watson, C. J. Concerning Urobilinogen. An Improved Method for the Approximate Quantitative Estimation of Urobilinogen in Urine and Feces, *Am J Clin Path* 6:458, 1936

<sup>18</sup> Ham, T. H. Studies on Destruction of Red Blood Cells. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, Investigation of Mechanism of Hemolysis with Observations on Five Cases, *Arch Int Med* 64:1271 (Dec) 1939

## COMMENT

The serologic studies reported afford a rational explanation of the patient's illness. It seems reasonable to suggest a similarity of the action of the cold hemagglutinin *in vivo* to that observed *in vitro*. This is shown by the observation of erythrocyte agglutination in the capillaries of the conjunctiva after this was cooled. It is to be expected, then, that marked cooling of the body in any position will be followed by hemagglutination. Both the *in vivo* and the *in vitro* experiments indicated the rapidity of this reaction at a low temperature and its prompt disappearance as the temperature rose. The episodes of tingling of the hands and feet that the patient noticed on exposure to cold can reasonably be explained on this basis.

The fact that the patient never experienced symptoms of vascular insufficiency in the lobes of the ears or tip of the nose at low temperatures or in the tongue or pharynx after ingestion of a cold drink cannot be explained. Some patients described in the literature as having a cold agglutination titer lower than our patient's presented such symptoms. The localization of the symptoms to the fingers and toes is in part explained by a normal large temperature gradient in these parts. A fall in temperature in the fingers and toes on exposure of the entire body to cold is a normal phenomenon.<sup>19</sup> It should be emphasized that we were not able to find any evidence of organic vascular disease, such as arteriosclerosis or thromboangitis obliterans. Many patients with a relatively high titer of cold hemagglutination never have symptoms of arterial insufficiency.

The last attack, the one resulting in acroangrene, was apparently similar to the previous ones, differing quantitatively in that the cold was more severe and persisted for a longer period. It would appear that at this time the intense agglutination occluded many small peripheral blood vessels interfering with, or stopping, the blood flow. The period of vascular insufficiency was so prolonged that organic ischemic changes occurred in the vessels and the tissues of these regions. Capillary thrombosis was the probable result. Finally, even with rewarming of the part, when the agglutination should have broken up, reestablishment of the circulation could not be effected and dry gangrene resulted. That such a phenomenon might occur was predicted by Amzel and Hirsfeld.<sup>20</sup>

There are numerous other conditions in which episodes of arterial insufficiency of the extremities occur despite the absence of disease of the larger arteries. In severe anemia the oxygen-carrying capacity of the blood is so reduced as to give rise to tingling and other sensations. Similar symptoms are common in polycythemia vera, in which the viscosity of the blood may play an important role. A report<sup>21</sup> of the occurrence of Raynaud's syndrome in association with multiple myeloma with hyperglobulinemia indicates that intense rouleau formation may at times interfere with circulation. Cases reported as instances of chronic acrocyanosis have been characterized by long-standing coldness and cyanosis of the fingers and toes which might progress to gangrene. A recently observed case<sup>22</sup> of marked mitral stenosis with superimposed acute bacterial endocarditis was characterized by coldness and cyanosis of the digits. Similar phenomena<sup>23</sup> have been observed in cases of ball valve thrombosis of the left auricle associated with

19 Lewis, T. Observations on Some Normal and Injurious Effects of Cold upon the Skin and Underlying Tissues, *Brit M J* 2 795, 1941

20 Amzel, R., and Hirsfeld, L. Ueber die Kalteagglutination der roten Blutkörperchen, *Ztschr f Immunitätsforsch u exper Therap* 43 526, 1925

21 Wintrobe, M. M., and Buell, M. V. Hyperproteinemia Associated with Multiple Myeloma, *Bull Johns Hopkins Hosp* 52 156, 1933

22 Personal observation of the authors

23 Fishberg, A. M. Heart Failure, Philadelphia, Lea & Febiger, 1940

mitral stenosis In such cases the arterial insufficiency of the extremities is due to obstruction of the circulation at the mitral orifice "Epinephrine shock," with marked coldness, pallor and cyanosis of the extremities, has been described as a manifestation of severe prolonged crises in cases of pheochromocytoma of the adrenal medulla<sup>24</sup> In shock, or circulatory collapse due to severe injury from burns or other causes, insufficiency of the peripheral circulation is due to pooling of the blood in the splanchnic area Finally, there is that group of conditions classified as Raynaud's syndrome, in which a vasomotor disturbance may be responsible for the ischemia<sup>25</sup>

The occurrence of dry gangrene of the digits in the presence of normal pulsations of the larger arterial vessels is rare Case 2 of Nygaard and Brown<sup>26</sup> is one of gangrene of the toes of undetermined cause, though the authors demonstrated an abnormality in the coagulation of the blood Lewis<sup>27</sup> discussed this syndrome, mentioning the unusual appearance of gangrene in syphilitic paroxysmal hemoglobinuria, in which functional vasomotor phenomena are common Under the heading of "Bilateral Gangrene of the Digits in the Young and in the Elderly" he mentioned the relationship to acute infections, wasting diseases and Raynaud's syndrome He did not include cold hemagglutination as a cause of symmetric gangrene Symmetric gangrene associated with widespread purpura was reported by Fatheree and Hines<sup>28</sup> Symmetric gangrene due to vasospasm is a common occurrence in epidemics of ergotism<sup>29</sup> Similar gangrene has been reported as following the use of ergotamine tartrate for the relief of pruritis<sup>30</sup> We are omitting from this discussion the effect of physical agents as a cause of gangrene A review of all the published cases of cold hemagglutination reveals 12 instances of functional vasomotor disturbances of the extremities<sup>31</sup> and 1 instance of gangrene<sup>4</sup> In our case gangrene was more extensive than in the one previously reported

Though we were never able to reproduce the hemoglobinuria, we have no doubt that it occurred many times, as stated by the patient The result of the *in vivo*

24 Engel, F L, Mencher, W H, and Engel, G L "Epinephrine Shock" as a Manifestation of a Pheochromocytoma of the Adrenal Medulla, *Am J M Sc* **204** 649, 1942

25 Hunt, J H Raynaud Phenomena Critical Review, *Quart J Med* **5** 399, 1936

26 Nygaard, K K, and Brown, G E Essential Thrombophlebitis, *Arch Int Med* **59** 82 (Jan) 1937

27 Lewis, T Vascular Disorders of the Limbs Described for Practitioners and Students, New York, The Macmillan Company, 1936

28 Fatheree, T J, and Hines, E A, Jr Symmetrical Gangrene of Extremities Associated with Purpura, *Am Heart J* **12** 235, 1936

29 Barger, G Ergot and Ergotism, London, Gurney & Jackson, 1931

30 Yater, W, and Cahill, J A Bilateral Gangrene of the Feet Due to Ergotamine Tartrate Used for Pruritis of Jaundice, *J A M A* **106** 1625 (May 9) 1936

31 (a) Iwai, S, and Meisai, N Etiology of Raynaud's Disease, *Japan M World* **5** 119, 1925 (b) Alexander, H L, and Thompson, L D Autohemagglutination in Chronic Leukemia, *J A M A* **85** 1707 (Nov 28) 1925 (c) Iwai and Meisai<sup>9</sup> (d) Steffel, R Etude des hemoglobinuries, Thesis, Paris, Louis Arnette, 1928 (e) Davidson, L S P Macrocytic Haemolytic Anemia, *Quart J Med* **1** 543, 1932 (f) Roth, G Paroxysmal Hemoglobinuria with Vasomotor and Agglutinative Features, *Proc Staff Meet, Mayo Clin* **10** 609, 1935 (g) Salén, E B Thermostabiles nicht komplexes (Auto-) Hamolysin bei transitorischer Kalthämoglobinurie, *Acta med Scandinav* **85** 570, 1935 (h) Hanns, A, and Sommer, A Acrocyanose, auto-agglutination des hématies, hemoglobinurie paroxystique, *Strasbourg med* **98** 172, 1938 (i) Gautier, C, Heimann, V, and Laudat, M Grande auto-agglutination des hématies Lymphome splénique Crises de cyanose Action remarquable de la radiothérapie sur le déséquilibre des albumines du sérum, *Bull et mem Soc méd d hôp de Paris* **55** 59, 1939 (j) Benians, T H C, and Feasby, W R Raynaud's Syndrome with Spontaneous Cold Hemagglutination, *Lancet* **2** 479, 1941 (k) Sezary, A, Kipfer, H, and Gharib, M "Livedo annularis" et crises de cyanose chez un sujet atteint de maladie hemolytique avec grande auto-agglutination des hématies, *Bull et mem Soc med d hop de Paris* **54** 1710, 1938

experiment in which the aim was cooled indicates that marked hemoglobinemia occurred locally at the site of action of the agglutinin. When such a process was widespread, even if the hemoglobinemia in any one site was not so great as in the experiment, the probability of hemoglobinuria would be increased. In addition to the present case, hemoglobinuria in association with cold hemagglutination was reported in 17 cases<sup>32</sup>. It is not possible to say how often a pathogenetic relationship existed between the hemoglobinuria and the cold hemagglutination in these reported cases. Several were instances of acute hemolytic anemia. It is well known that hemoglobinuria in the absence of cold hemagglutination may occur in such states.

When a clearcut relationship between cold and hemoglobinuria can be shown, it is likely that the cause of the hemoglobinuria is in the activation of the cold hemagglutinin. However, when hemoglobinuria occurs at room temperature, or even at a higher temperature, there is good reason to doubt a close causal relationship between the hemoglobinuria and a cold hemagglutinin which may be present. In no case of hemolytic anemia with hemoglobinuria and cold hemagglutination has the close dependence of the hemoglobinuria on a fall in temperature been demonstrated. Some of the patients with hemolytic anemia due to a sulfonamide compound were febrile before or at the onset of the hemolytic process. There is a definite possibility that the phenomenon of cold hemagglutination in certain instances of hemolytic anemia may be unrelated to the mechanism of hemoglobinuria.

Besides the fact that hemoglobinuria may occur in the absence of cold hemagglutination is the knowledge that there are numerous examples of cold hemagglutinins of high titers without hemoglobinuria.

#### SUMMARY AND CONCLUSIONS

A case of symmetric gangrene of the tips of the extremities due to cold hemagglutination is described.

Experimental studies revealed (a) unilateral hemoglobinemia following exposure of a forearm to cold, (b) hemagglutination in the capillaries of the conjunctiva due to cold and (c) absence of syphilis or evidence of a hemolytic anemia. No cause could be found to explain the presence of the cold hemagglutinin.

A discussion is presented of clinical conditions in which transient or permanent arterial insufficiency of the extremities occurs despite adequate pulsation and absence of disease of the peripheral arteries.

All the cases of cold hemagglutination reported in the literature in association with arterial insufficiency of the extremities or hemoglobinuria are tabulated.

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32 (a) Mino, P. *Einiges über Konstitutionslehre und serologische Forschung*, Deutsche med Wchnschr **50** 1533, 1924. (b) Kopplin, F. *Autohemagglutination und Anämie*, Ztschr f klin Med **130** 784, 1936. (c) Watson, C. J. *Hemolytic Jaundice and Macrocytic Hemolytic Anemia*, Ann Int Med **12** 1782, 1939. (d) Antopol, W., Applebaum, I., and Goldman, L. *Two Cases of Acute Hemolytic Anemia with Auto-Agglutination Following Sulfanilamide Therapy*, J A M A **113** 488 (Aug 5) 1939. (e) Reisner, E. H., and Kalkstein, M. *Auto-Hemolytic Anemia with Autoagglutination. Improvement After Splenectomy*, Am J M Sc **203** 313, 1942. (f) Rothstein, I., and Cohn, S. *Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy*, Ann Int Med **16** 152, 1942. (g) Dameshek, W. *Cold Hemagglutinins in Acute Hemolytic Reactions Following Sulfonamide Medication and Infection*, J A M A **123** 77 (Sept 11) 1943. (h) McCombs and McElroy<sup>4</sup>. (i) Alexander and Thompson<sup>31b</sup>. (j) Stieffel<sup>31d</sup>. (k) Roth<sup>31f</sup>. (l) Salen<sup>31g</sup>. (m) Hanns and Sommer<sup>31h</sup>.



# Progress in Internal Medicine

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## VASCULAR DISEASES

### NINTH ANNUAL REVIEW

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### REVIEW OF SOME OF THE RECENT LITERATURE

The present review was obviously compiled under wartime conditions, and many articles have been omitted because the journals were not available for study. These are known to us and will be included in future reviews. Although there has not been a noticeable decline in original material during the past year, it is anticipated that such a condition will prevail as more and more investigators enter military service or attend to their busy wartime practices. Dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) has been given considerable attention in this review, and the many articles on heparin have been omitted pending decision as to their value when this drug is finally compared with the former compound.

### PHYSIOLOGY

The causative factor responsible for pain in an ischemic extremity has been subject to considerable controversy. Harpruder and Stein<sup>1</sup> report their observations on the genesis of ischemic pain, substantiating in part the theory of the so-called P substance as the responsible agent. Their studies were done in the usual manner. Pain was produced by movements of the fingers of an arm made ischemic by a blood pressure cuff inflated to 200 mm of mercury. Before the cuff was inflated an average of forty contractions of the fingers was possible before pain developed. After the cuff was inflated and the arm rendered ischemic, only one-third to one-half the same number of contractions were possible. With this as a control experiment, other studies were performed as follows. It was first noted that pain could not be transferred from the lower to the upper extremities. This was demonstrated by producing an ischemic pain in the lower extremities, releasing the pressure and within forty seconds repeating the previously mentioned control experiment. No change in pain threshold was noted. The authors were next able to ascertain a phase of recovery, namely, three to five minutes could elapse between experiments and similar results be obtained. When the ischemic extremity was immersed in a water bath at a temperature of 115 F, pain rapidly developed, similar to that produced with exercise. Pain did not develop

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1 Harpruder, K, and Stein, I D. Studies on the Nature of Pain Arising from an Ischemic Limb. I. Clinico-Experimental Observations, *Am Heart J* **25** 429 (April) 1943.

when the arm was immersed in cold water. Since certain investigators have considered vasodilatation as a cause for pain in ischemia, the authors dilated the vessels of the upper extremities reflexly and then rendered one arm ischemic, they found little change from the pain threshold of the control experiment. Oxygen likewise had little influence on the pain, as no change could be elicited in patients artificially rendered anoxic. Of interest were the reflex secondary effects of exercising the ischemic extremity. Both the systolic and the diastolic pressure were greatly elevated after exercise, usually returning to normal after two minutes' rest.

In a second article<sup>2</sup> is a report of chemical studies performed on venous blood obtained before the experiment, when pain developed and after the recovery phase. Lactic acid increased with exercise and further increased during the recovery phase, which indicates that there is no relationship between the concentration of this substance and the pain. The concentrations of histamine, ammonia and epinephrine in the blood and the oxidation potential and the conductivity of serums were also determined, but no essential change was shown. Serum potassium was of particular interest, because it was found to be elevated only during the period of pain. When potassium was injected intra-arterially the pain was so intense that only a few subjects were submitted to this procedure. The authors concluded that potassium plays a major role in the genesis of ischemic pain, most likely by its liberation from the cells and rapid accumulation in sufficient concentration to stimulate the pain end organs in muscle.

*Capillaries*—Eichna and Bordley<sup>3</sup> studied the digital capillary blood pressure in normal and in hypertensive subjects and found it to vary within wide limits but to be qualitatively and quantitatively similar in the two groups. Under such physiologic influences as neurogenic vasoconstriction, reactive hyperemia, reflex vasodilatation and variations in cutaneous temperature between 27 and 35 C (80.6 and 95 F), small changes in capillary pressure were noted but the resultant values did not fall beyond "resting" limits. Only during increases in local venous pressure did the digital capillary blood pressure consistently exceed "resting" values. Wide variations in digital capillary blood pressure persisted during reflex vasodilatation, a state during which digital circulation is considered to be full, standard and reproducible. During vasodilatation, induced either reflexly or by locally injected histamine, there was a disproportionately greater increase in pressure in the venous limb than elsewhere in the capillary. The other states all influence the digital capillary blood pressure equally in all portions of the capillary. No correlation existed between the digital capillary blood pressure and arterial pressure except perhaps during the hyperemia induced by histamine. The similarity of the digital capillary blood pressure of normal and that of hypertensive subjects indicates that in the digits the increased vascular resistance of hypertensive subjects is pre-capillary, presumably arteriolar.

Eichna<sup>4</sup> also compared the digital capillary pressure in hypertension induced by paredrinol sulfate (*α*-N-dimethyl-*p*-hydroxyphenylthylamine sulfate) with normal arterial pressure. He found them to be essentially the same. This observation

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2 Harpruder, K, and Stein, I. D. Studies on the Nature of Pain Arising from an Ischemic Limb. II. Biochemical Studies, *Am Heart J* **25** 438 (April) 1943.

3 Eichna, L. W., and Bordley, J. Capillary Blood Pressure in Man. Direct Measurements in the Digits of Normal and Hypertensive Subjects During Vasoconstriction and Vasodilatation Variously Induced, *J Clin Investigation* **21** 711 (Nov) 1942.

4 Eichna, L. W. Capillary Blood Pressure in Man. Direct Measurements in the Digits During Arterial Hypertension Induced by Paredrinol Sulfate, *J Clin Investigation* **21** 731 (Nov) 1942.

was equally true for capillaries of digits with intact innervation and for those of persons who had undergone preganglionic sympathectomy. At the height of the paredrinol-induced hypertension, the vasodilatation of local hyperemia did not significantly alter the digital capillary blood pressure. The hyperemia of the histamine flare was usually associated with a rise in the digital capillary blood pressure to a value which just exceeded the pressure obtained during the resting state at both normal and elevated arterial pressures.

Neumann, Cohn and Burch have continued their studies on the reactions of the small vessels following application of sensory stimuli at distant parts of the body. Their methods for measuring the spontaneous variations in the volumes of fingers and toes have been described in previous reviews. In one recent study<sup>5</sup> they stress the importance of the conditions under which these experiments are to be undertaken, such as uniform temperature, humidity and state of digestion. These are well known to investigators in this field, but the authors show objective evidence to support the belief that the patient's mental comfort and the degree of his relaxation are equally important. This was demonstrated by converting a "laboratory" into a conventional bedroom and by observing how the frequency of reaction on the part of the peripheral vessels increased when sensory stimuli were applied. Studies were performed on persons under both types of environment. In many instances better reactions were obtained in the hypertensive or senile patients after a simple change in atmosphere. These subjects frequently had reactions similar to normal subjects because of their ability to relax in a more suitable atmosphere. The same authors, in a study reported in a second communication,<sup>6</sup> found the mean reaction times of the tips of the fingers of normal persons to be 3.12 seconds, of senile persons 3.86 seconds and of hypertensive subjects 2.94 seconds. For the tips of the toes of the same subjects the times were more prolonged, being 3.43, 4.25 and 3.24 seconds respectively, but the delay is of the same order of magnitude in each of the three groups when compared with the values for the fingers. The authors accounted for this difference on the basis of the time required for the efferent impulses to traverse the additional length of postganglionic sympathetic fibers in order to reach the toes. The reason for the differences in each group of patients could not be explained excepting on the basis of changes in the vessels themselves or of a factor outside the vessels, such as the nervous system or a chemical state which influences the vessels.

In a previous review the reactive hyperemia ring test of Di Palma and others was described. This procedure was used to measure the ability of the smallest blood vessels of the skin to respond to local ischemia followed by a reactive hyperemia. By noting the time required for the area of ischemia to clear, a direct indication of the rate of local flow is obtained. The time required for local ischemia is designated the threshold time, and that required for clearing, the clearing time. All measurements are recorded in seconds with a standard stopwatch. The test was later termed the capillary sensitivity test. In brief, it is a more scientific version of the older method of applying pressure to the skin with a finger and noting the time required for the ischemic imprint to fade to the color of the surrounding skin.

5 Neumann, C., Cohn, A. E., and Burch, G. E. A Study of the Influence of the Character of an Examining Room on the Peripheral Blood Vessels of Normal, Hypertensive, and Senile Subjects, *J. Clin. Investigation* **21**: 651 (Nov.) 1942.

6 Burch, G. E., Cohn, A. E., and Neumann, C. Reactivity of Intact Blood Vessels of the Fingers and Toes to Sensory Stimuli in Normal Resting Adults, in Patients with Hypertension, and in Senile Subjects, *J. Clin. Investigation* **21**: 655 (Nov.) 1942.

In the first of a series of new articles Di Palma and Foster <sup>7</sup> note the segmental and aging variations of reactive hyperemia in human skins. The threshold and clearing times were ascertained in fourteen dorsal and fifteen ventral positions, covering all the cutaneous branches of nerve segments from the ophthalmic division of the fifth cranial nerve to the fifth sacral nerve. It was noted that the more caudal the nerve segment, the higher the threshold and clearing times. With advancing age similar results were obtained but the gradient was marked and practically limited to the lower extremities. In another article, Di Palma, Muss and Foster <sup>8</sup> compare their readings obtained by this test on 24 patients suffering from arteriosclerosis obliterans with the oscillometric index and the results of thermometric and histamine flare tests. As the ring test showed the state of the circulation in the superficial vessels, the investigators obviously were unable to correlate the readings secured in this test with those obtained with the oscillometer, but they were in agreement with those obtained with histamine. It was not unusual to obtain normal results in reactive hyperemia ring tests over the ankle and foot, considering the age of the patient, even in advanced stages of obliteration of arterial trunks. On the other hand, the test was useful from a prognostic standpoint, in that the results were directly proportional to the symptoms, they paralleled collateral circulation and the clearing time was greatly prolonged in gangrenous areas. The test appears to be another means for evaluating the function of the fine vessels of the skin.

In their studies reported in a third article Di Palma and Foster <sup>9</sup> were unable to demonstrate any differences in response between the small dermal vessels of normal persons and of patients with benign hypertension, with hypertension associated with arteriosclerosis, or with uncomplicated arteriosclerosis. On the other hand, of 11 patients with malignant hypertension 10 had a response of the small vessels which indicated greatly decreased sensitivity. Thirteen patients with hypertension complicated by neurologic disorders were found to have cutaneous vessels as much as eighteen times more sensitive than those of persons in the normal and the other hypertensive groups. The authors concluded that the humoral agent now believed responsible for arterial hypertension does not exert its influence on the smallest vessels in the benign stages of the disease but may do so in a later, malignant phase.

Di Palma <sup>10</sup> also noted the responsiveness of the smallest blood vessels of the human skin in systemic anoxemia, hypercapnia, acidosis and alkalosis. His observations demonstrated that systemic anoxemia causes a decrease in sensitivity to local ischemia and a slowing of blood flow, whereas hypercapnia is capable of preventing these changes. With systemic acidosis there is a decrease in sensitivity to local ischemia and a slowing of blood flow. The exact opposite takes place in systemic alkalosis. These changes usually occurred independently of changes in

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7 Di Palma, J. R., and Foster, F. I. The Segmental and Ageing Variations of Reactive Hyperemia in Human Skin, *Am Heart J* **24** 332 (Sept) 1942

8 Di Palma, J. R., Muss, I., and Foster, F. I. A Reactive Hyperemia Ring Test in the Study, Evaluation and Prognosis of Pedal Lesions Caused by Arteriosclerosis Obliterans and Arterial Embolism, *Am Heart J* **24** 345 (Sept) 1942

9 Di Palma, J. R., and Foster, F. I. Sensitivity of Smallest Cutaneous Blood Vessels: Quantitative Responses to Graded Mechanical Stimulation and to Local Ischemia in Arterial Hypertension, Arteriosclerosis, and Certain Allied Disorders, *J Clin Investigation* **21** 675 (Nov) 1942

10 Di Palma, J. R. Quantitative Alterations in the Hyperemia Responses to Local Ischemia of the Smallest Blood Vessels of the Human Skin Following Systemic Anoxemia, Hypercapnia, Acidosis, and Alkalosis, *J Exper Med* **76** 401 (Nov) 1942

pulse rate, blood pressure and respiratory rate and depth. Di Palma advances the view that the carbon dioxide concentration in the blood, or something directly associated with it, is the most important factor determining the sensitivity of these vessels, rather than oxygen saturation or changes in  $p_{H_2}$ .

Hertzman and Roth<sup>11</sup> demonstrated the selective effects of local cold on the terminal pad vessels and the digital artery of the chilled finger by means of their photoelectric plethysmograph. The digital artery does not participate in the vasoconstrictor reflexes elicited by the cold, but it will ultimately constrict if cold is continued, owing to the direct effects of the fall in temperature on the artery. Reactive dilatation also takes place in the reverse order, as the digital artery will finally relax when the rise in temperature of the finger permits relaxation of this artery. In a few normal subjects the reactive dilatation produced a pad pulse similar to that seen in chronic hypertension. This suggested to the authors that one of the factors responsible for the change in pad pulse form in hypertension may be the shunting of blood through direct arteriovenous communications.

The same authors<sup>12</sup> performed a number of experiments to demonstrate the absence of vasoconstrictor reflexes in the forehead. They were unable to obtain spontaneous rhythmic constrictions of vasomotor origin over this area, even though they were readily obtained in the finger. Also lacking were the usual vasoconstrictor reflexes elicited by startle, awakening, a deep breath, immersion of the hand in ice water or local application of cold. The responses in the forehead resembled those in a sympathectomized digit. Constriction is gradual after cold is applied locally but appears to be due to the direct effects of cold on the vessels. In addition, the reactive dilatation to cold which occurs in the fingers was not observed in the skin of the forehead.

Weatherby<sup>13</sup> reinvestigated the problem of the effect of smoking on the cutaneous temperature, taking into consideration certain physical and physiologic factors which had been overlooked in other investigations. Under ordinary conditions the smoking of a cigaret by the average habitual smoker (who inhales) results in a rise in the systolic and diastolic blood pressure of 10 to 25 mm of mercury, an increase in pulse rate of 5 to 20 beats per minute, a drop in the temperature of the skin of the finger of 2 to 5 degrees C (3.6 to 6 degrees F) and of the toes of 3 to 7 C (5.4 to 12.6 degrees F). Occasionally greater changes occur in hyperactive subjects. The smoking of a cigaret by the average nonsmoker (without inhaling) causes only slight changes at most. The maximum vasoconstriction rarely persists for more than a few minutes. An environmental temperature of 30 C inhibits almost completely the peripheral vasoconstriction caused by smoking. Smoking will also delay the warming of the skin of the feet after a cold foot bath. Drinking cold water has the same effect. Nicotine was shown to be the most important agent in causing these changes as when it was completely removed from the cigaret none of the phenomena just mentioned occurred and when it was restored to the original cigaret they were again noted. The author was unable to lower the temperature of the skin by altering the nature of the respiratory movement, but various physiologic and psychic stimuli, such as reading, talking, hearing sudden noises, drinking cold water and hyperventila-

11 Hertzman, A. B., and Roth, L. W. The Vasomotor Components in the Vascular Reactions in the Finger to Cold, *Am J Physiol* **136** 669 (June) 1942.

12 Hertzman, A. B., and Roth, L. W. The Absence of Vasoconstrictor Reflexes in the Forehead Circulation: Effects of Cold, *Am J Physiol* **136** 692 (June) 1942.

13 Weatherby, J. H. Skin Temperature Changes Caused by Smoking and Other Sympathomimetic Stimuli, *Am Heart J* **24** 17 (July) 1942.

tion, may cause changes in cutaneous temperature comparable to those produced by smoking. Mild physical activity, even at relatively low atmospheric temperatures, inhibits the fall in cutaneous temperature after smoking. The author concluded from these studies that it is difficult to determine what effect smoking has on the average person, since the conditions under which a person lives are not comparable to the conditions in the laboratory or the hospital where the experiments are performed.

*Blood Flow*—Abramson, Fierst and Flachs<sup>14</sup> studied the rate of peripheral blood flow in a series of 19 patients who had edema either in a single upper or lower extremity or in both lower limbs. As in previous studies, the venous occlusion plethysmograph method was used. Separate measurements were made in the hand, forearm and leg. They noted that the peripheral circulation in edematous extremities unassociated with organic heart disease was mainly increased and certainly not decreased. When the edema was associated with congestive heart failure the readings on the edematous limbs fell within the range of those obtained for normal subjects. The authors are of the opinion that anoxia resulting from the edema or from the accumulation of vasodilator substances locally or from both of these factors might be effective in producing arteriolar vasodilatation and an increase in blood flow to the part.

The same authors,<sup>15</sup> using the same method of study, noted the rate of peripheral blood flow during rest and the circulatory response to exercise in a series of 25 patients with aortic insufficiency and in 16 subjects with mitral valvular disease. The average circulation in the hand was found to be somewhat diminished in both series of patients, while the readings for the forearm and leg fell within normal limits. The postexercise response of the blood vessels in the forearm to a specific amount of work was found to be greater than in the control group. The authors thus concluded that in the majority of patients with aortic insufficiency or mitral valvular disease there is no evidence to be found of excessive vasodilatation or vasoconstriction in the vessels of the forearm or leg.

Abramson and his associates<sup>16</sup> also demonstrated that the blood flow in the paralyzed limbs of 27 subjects with acute or chronic anterior poliomyelitis was the same as in the contralateral normal extremity. Evidence is presented, moreover, to substantiate the knowledge that the vessels of the diseased limb were more sensitive to cold than those of the normal limb. In a similar manner, Abramson, Fierst and Flachs<sup>17</sup> studied the peripheral circulation in 11 patients with various types of anemia. A moderate increase in blood flow was observed in the forearm, but in the hand the readings were, for the most part, within the lower range of normal or somewhat decreased. Studies of blood flow were also performed on 9 patients after the administration of mecholyl chloride (acetylbetamethylcholine chloride) by iontophoresis<sup>18</sup>. A significant increase in the rate of blood flow in the

14 Abramson, D I, Fierst, S M, and Flachs, K. Rate of Peripheral Blood Flow in the Presence of Edema, *Am Heart J* **25** 328 (March) 1943.

15 Abramson, D I, Fierst, S M, and Flachs, K. Effect of Muscular Exercise upon the Peripheral Circulation in Patients with Valvular Heart Disease, *J Clin Investigation* **21** 747 (Nov) 1942.

16 Abramson, D I, Flachs, K, Freiberg, J, and Mirsky, I A. Blood Flow in Extremities Affected by Anterior Poliomyelitis, *Arch Int Med* **71** 391 (March) 1943.

17 Abramson, D I, Fierst, S M, and Flachs, K. Resting Peripheral Blood Flow in the Anemic State, *Am Heart J* **25** 609 (May) 1943.

18 Abramson, D I, Fierst, S M, and Flachs, K. Evaluation of the Local Vasodilator Effect of Acetyl-Beta-Methylcholine Chloride (Mecholyl) by Iontophoresis, *Am Heart J* **23** 817 (June) 1942.

forearm and the foot was noted, which continued for some time after the treatment was terminated. The effect on the leg was less marked. The increase in flow was considered to be primarily the result of vasodilatation of cutaneous blood vessels, those in the muscles probably contributing little if at all to the effect.

Lastly, Abramson and Fierst<sup>19</sup> studied the arterial blood flow in patients with uncomplicated varicose veins. The flow was found to fall within the range for normal subjects or somewhat beyond it. The authors are of the opinion that the various cutaneous lesions associated with varicosities do not have their origin in a diminished arterial inflow.

Friedland, Hunt and Wilkins<sup>20</sup> were unable to find an increased blood flow in a limb during rises in venous pressure. In this study the blood flow in the extremities of human beings was measured with and without local venous congestion produced by inflating blood pressure cuffs on the proximal parts of the limb. Four different methods were used: capillary microscopy, venous blood oxygen analysis, measurements of cutaneous skin temperature and determinations with the plethysmograph. The observations presented in this paper have undoubtedly caused considerable discussion and are contrary to the current opinion at this time but they are lending support to a small but growing group of investigators who doubt the efficiency of the intermittent venous occlusion type of therapy. The stretching effect on the venocapillary bed, however, is readily demonstrated.

Evans and Stewart<sup>21</sup> report their measurements of the peripheral blood flow on a patient with an adrenal pheochromocytoma before operation and at intervals for one year afterward. They used the method previously described by Stewart and Jack and by Stewart and Evans for their determinations. Postoperatively the patient had an average increase of 60 per cent in the amount of blood allotted to the peripheral circulation. The basal metabolic rate decreased from plus 48 to an average of minus 15 after the operation. Additional studies revealed a longer circulation time, an increased cutaneous temperature, a decreased rectal temperature and a fall in blood pressure and in pulse rate following the operation.

Warren and his colleagues<sup>22</sup> studied the blood flow in the arm of a normal person in whom procaine hydrochloride had been injected by the paravertebral route into the sympathetic ganglions supplying the right upper extremity. Observations were made on two separate occasions, and measurements were taken before, during and after the anesthetization. Complete absence of vasomotor activity in response to sensory stimuli on deep inspiration indicated complete paralysis of the sympathetic ganglions supplying the right hand. This paralysis produced a striking increase in blood flow. After the effect of the procaine had passed away, the right hand was immersed in water at a temperature of 43 C. Local heat produced the same increase in blood flow in the right hand as had paralysis of the sympathetic ganglions. The fact that a complete blocking of the sympathetic ganglions produces full vasodilatation in the hand demonstrated to the authors that inhibition of sympathetic activity is sufficient to explain the vasodilatation.

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19 Abramson, D. I., and Fierst, S. M. Arterial Blood Flow in Extremities with Varicose Veins, *Arch Surg* **45** 964 (Dec) 1942.

20 Friedland, C. K., Hunt, J. S., and Wilkins, R. W. Effects of Changes in Venous Pressure upon Blood Flow in the Limbs, *Am Heart J* **25** 631 (May) 1943.

21 Evans, W. F., and Stewart, H. J. The Peripheral Blood Flow in a Case of Adrenal Pheochromocytoma Before and After Operation, *Am Heart J* **24** 835 (Dec) 1942.

22 Warren, J. V., Walter, C. W., Romano, J., and Stead, E. A., Jr. Blood Flow in the Hand and Forearm After Paravertebral Block of the Sympathetic Ganglia. Evidence Against Sympathetic Vasodilator Nerves in the Extremities of Man, *J Clin Investigation* **21** 665 (Nov) 1942.



which occurs in the hand when the body is heated. The authors saw no necessity for postulation that the sympathetic nerves to the hand contain vasodilator fibers.

In the forearm, paravertebral injection of procaine hydrochloride into the sympathetic ganglions caused a sixfold increase in blood flow. A similar increase in blood flow was produced by immersing the forearm in hot water. This indicates again that the removal of all sympathetic impulses to the vessels of the forearm produces as great rise in blood flow as does heating the part. Inhibition of vasoconstriction alone can explain the phenomenon. The fact that neither heating the forearm nor injection of procaine into the sympathetic ganglions produced maximal dilatation in the forearm indicated to the authors that many of the vessels of the forearm are not under the control of the sympathetic nervous system. They suggested that the vessels of the skin of the forearm are under the control of the sympathetic nervous system and that those of the muscle are not.

*Diagnostic Tests*—Goetz<sup>23</sup> describes a new ergograph with which a claudication index can be ascertained. Studies were made on normal persons as well as on patients with intermittent claudication. For 97 per cent of those with claudication the index was below 40. This apparatus appears simple, and the claudication index affords considerable opportunity for investigators interested in evaluating various therapeutic agents.

*Circulation Time*—Hussey, Cyr and Katz<sup>24</sup> compared solutions of alpha lobeline, calcium gluconate and magnesium sulfate for purposes of measuring the circulation time from the arm to the tongue. The measurements were made on 50 normal persons and on 50 patients with heart failure. Alpha lobeline gave somewhat shorter measurements than calcium gluconate and magnesium sulfate for both groups of subjects but failed to provide an end point more often than either of the other drugs. Furthermore, the fact that it sometimes measured the arm to lung circulation time seems to detract from its value for routine use. Its chief advantage consists in the objectivity of its end point. Calcium gluconate and magnesium sulfate gave approximately equal results. They seem to be equally valuable for routine use in measurements of the arm to tongue circulation time, and perhaps are more valuable in this respect than alpha lobeline.

Elek and Solarz<sup>25</sup> have added papaverine to the numerous agents used for measuring circulation time in man. They consistently obtained a sudden deep inspiration after the injection of 40 mg (1.25 cc) of papaverine hydrochloride intravenously. The arm-respiratory center circulation time was thus obtained, as with sodium cyanide. The average time for 50 normal persons without evidence of heart failure was 20.8 seconds, the range extending from 15.4 to 27.0 seconds.

Wilburne<sup>26</sup> reinvestigated the problem of the effects of posture on the circulation time, using calcium gluconate and measuring the velocity of blood flow from the arm to the tongue. In his studies, the time was measured with the patient in the recumbent position and again with the patient comfortably sitting with both

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23 Goetz, R. H. Ergographic Studies. Description of New Device, and Observations on Normal Subjects and on Patients with Intermittent Claudication, *Am Heart J* **23** 782 (June) 1942.

24 Hussey, H. H., Cyr, D. P., and Katz, S. The Comparative Value of Calcium Gluconate, Magnesium Sulfate, and Alpha Lobeline Hydrochloride as Agents for Measurements of the Arm to Tongue Circulation Time in Fifty Patients With and Fifty Patients Without Heart Failure, *Ann Int Med* **17** 849 (Nov) 1942.

25 Elek, S. R., and Solarz, I. D. The Use of Papaverine as an Objective Measure of Circulation Time, *Am Heart J* **24** 821 (Dec) 1942.

26 Wilburne, M. The Effects of Posture on the Velocity of Blood Flow from Arm to Tongue, *Am Heart J* **24** 816 (Dec) 1942.



legs dependent over the edge of the bed. A total of 73 measurements were taken. Two types of results were obtained. For patients whose circulation time in the recumbent position is normal, the value in the sitting position is higher, whereas for persons whose circulation time in the recumbent position is prolonged, the time in the upright position tends to be lower. The author believes that these findings substantiate the observations that the minute cardiac output is less in the sitting and standing positions than in the recumbent position. In the patients who already have a prolonged circulation time in the recumbent position, especially those with congestive heart failure, a change in position to the upright produces a pooling of blood in the lower extremities, lessens pulmonary congestion and decreases the circulation time.

#### DICOUMARIN

Link and his associates<sup>27</sup> were the first to isolate an active hemorrhagic agent from spoiled sweet clover, which is now known as dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]). Henceforth in this review it will be referred to as dicoumarin. This is a white crystalline substance slightly soluble in water but readily soluble in alkaline solution. The chemical experiments on it are too numerous to include in this review and will be omitted. Considerable pharmacologic and clinical studies have been reported, and these will be briefly reviewed.

This compound has been administered to hundreds of laboratory animals and used clinically on a large number of human beings and the reported results have been fairly consistent.<sup>28</sup> The authors agree that the effect of dicoumarin appears to be on prothrombin only. There is usually an associated delay in the coagulation time. The substance is active whether given orally or intravenously, and there is usually a lag of from twenty-four to seventy-two hours before the action of the drug is measurable. Fresh transfusions of serum or whole blood will cause a

27 Campbell, H. A., and Link, K. P. Studies on the Hemorrhagic Sweet Clover Disease. IV. The Isolation and Crystallization of the Hemorrhagic Agent, *J Biol Chem* **138**: 21 (March) 1941. Stahmann, M. A., Huebner, C. F., and Link, K. P. Studies on the Hemorrhagic Sweet Clover Disease. V. Identification and Synthesis of the Hemorrhagic Agent, *ibid* **138**: 513 (April) 1941.

28 (a) Bingham, J. B., Meyer, O. O., and Pohle, F. J. Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin). I. Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, *Am J M Sc* **202**: 563 (Oct) 1941. (b) Meyer, O. O., Bingham, J. B., and Pohle, F. J. The Effect of the Synthetic Dicoumarin 3,3'-Methylene-Bis-(4-Hydroxycoumarin) on the Prothrombin Time and Coagulation Time, *J A M A* **118**: 1003 (March 21) 1942. (c) Butt, H. R., Allen, E. V., and Bollman, J. L. A Preparation from Spoiled Sweet Clover [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood. Preliminary Report of Experimental and Clinical Studies, *Proc Staff Meet, Mayo Clin* **16**: 388 (June 18) 1941. (d) Barker, N. W., Butt, H. R., Allen, E. V., and Bollman, J. L. The Effect of 3,3'-Methylene-bis (4-Hydroxycoumarin) on Blood Coagulation Factors, *J A M A* **118**: 1003 (March 21) 1942. (e) Allen, E. V., Barker, N. W., and Waugh, J. M. A Preparation from Spoiled Sweet Clover [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood. A Clinical Study, *ibid* **120**: 1009 (Nov 28) 1942. (f) Prandoni, A., and Wright, I. The Anti-Coagulants, *Bull New York Acad Med* **18**: 433 (July) 1942. (g) Wright, I. S., and Prandoni, A. The Dicoumarin 3,3'-Methylene-Bis-(4-Hydroxycoumarin). Its Pharmacologic and Therapeutic Action in Man, *J A M A* **120**: 1015 (Nov 28) 1942. (h) Butsch, W. L., and Stewart, J. D. Clinical Experiences with Dicoumarin 3,3'-Methylene-Bis-(4-Hydroxycoumarin), *ibid* **120**: 1025 (Nov 28) 1942. (i) Townsend, S. R., and Mills, E. S. Effect of Synthetic Haemorrhagic Agent, 3,3'-Methylene-Bis-(4-Hydroxycoumarin), in Prolonging Coagulation and Prothrombin Time in Human Subject, *Canad M A J* **46**: 214 (March) 1942. (j) Davidson, C. S., and MacDonald, H. An Evaluation of the Use of Dicoumarin [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] as an Anticoagulant and Its Effect on Certain Plasma Constituents, *J Clin Investigation* **21**: 644 (Sept) 1942.

prompt lowering of the prothrombin and coagulation times, but occasionally this effect is not sustained and several transfusions may be necessary. Vitamin K has no effect on its prothrombin activity.

Pharmacologic studies reveal that it has no effect on hepatic or renal function, blood sugar, the erythrocyte or leukocyte count, the concentration of bilirubin or calcium in the blood serum, the value for nonprotein nitrogen in the blood, the icterus index, the fragility of the erythrocytes or the number of blood platelets. The sedimentation rate is usually increased, and the clot retraction is occasionally retarded. The bleeding time is not influenced, and although small doses have no influence on the coagulation time, larger doses tend to prolong it. There is considerable controversy as to the effect of this substance on the liver, especially after prolonged administration of fatal doses. When it has been administered correctly no demonstrable clinical evidence of hepatic disease has been noticed. Bingham, Meyer and Pohle<sup>28b</sup> report only moderate hydropic degeneration of the liver when fatal doses of dicoumarin were given. Rose, Harris and Chen<sup>29</sup> found central necrosis of the liver in about one half of the rats which had died of fatal doses. Postmortem studies made by Richards and Cortell<sup>30</sup> on a group of dogs, monkeys and guinea pigs that had received dicoumarin revealed necrosis of the liver. On the other hand, animals dying of spoiled sweet clover disease show no evidence of pathologic change in the liver. The majority of authors agree that the drug produces little, if any, damage to the liver and that when such damage is present it is usually secondary to local hemorrhage.

The mechanism by which dicoumarin causes hemorrhage appears to be fairly conclusive. It inhibits the action of prothrombin by destroying it or by inhibiting its production. If enough dicoumarin is given, the coagulation time is prolonged and bleeding may develop. It produces a hemorrhagic syndrome unlike any other type. Wright and Prandoni<sup>28c</sup> studied a number of patients who had received sufficient dicoumarin to produce this hemorrhagic tendency. They found the incidence of toxic reactions to be uninfluenced by age, sex or malnutrition. There was no increase in capillary fragility, no change in gastric acidity and no disturbance in renal or hepatic function. Davidson and MacDonald<sup>31</sup> were likewise unable to find a relationship between this abnormal clotting mechanism and other coagulation factors, namely foreign surface, platelets, "globulin substance" and plasma proteolytic enzyme. Like other investigators of this drug, they were unable to find any effect on the picture of the blood, hepatic function or plasma proteins. McGinty, Seegers, Pfeiffer and Loew<sup>32</sup> noted that purified beef prothrombin was capable of counteracting the hypoprothrombinemia induced in dogs by oral administration of dicoumarin. These authors considered the phenomena as purely a method of replacing the prothrombin, as the beef substance was as easily destroyed as the dogs' own plasma prothrombin.

The doses used by the various authors have been somewhat similar. Bingham and Meyer<sup>28b</sup> advise an initial dose of 5 mg per kilogram followed by daily administration of 1.5 mg per kilogram. They found that 4 mg per kilogram at intervals

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29 Rose, C. L., Harris, P. N., and Chen, K. K. Toxicity of 3,3'-Methylene-Bis-(4-Hydroxycoumarin), *Proc Soc Exper Biol & Med* **50** 228 (June) 1942.

30 Richards, R. K., and Cortell, R. Studies on Anticoagulant 3,3'-Methylene-Bis-(4-Hydroxycoumarin), *Proc Soc Exper Biol & Med* **50** 237 (June) 1942.

31 Davidson, C. S., and MacDonald, H. A Critical Study of the Action of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) (Dicoumarin), *Am J M Sc* **205** 24 (Jan) 1943.

32 McGinty, D. A., Seegers, W. H., Pfeiffer, C. C., and Loew, E. R. Plasma Prothrombin Concentration in Dogs Given 3,3'-Methylene-Bis-(4-Hydroxycoumarin) and Purified Beef Prothrombin, *Science* **96** 540 (Dec 11) 1942.

of three to five days was adequate to increase the prothrombin time when given intravenously. The latter method of administration was not recommended as it has no advantage over the oral route and does not shorten the latent period. Allen and his colleagues<sup>28c</sup> administered 200 to 300 mg on the first day, 200 mg on the second and additional on the third day if the prothrombin time warrants it. Wright and Piantoni<sup>28g</sup> administered 200 mg daily for three days, at which time an adequate prothrombin time was noted. Butsch and Stewart<sup>28h</sup> used 300 mg on two successive days and obtained the desired results. Two hundred milligrams on two successive days was recommended for children. Frequent determinations of prothrombin time are necessary and readings in excess of thirty-five seconds or 25 per cent of normal are unwise. Optimum levels are between thirty and thirty-five seconds, and if the level falls below thirty seconds a dose is indicated. The early signs of toxicity are usually lassitude and general malaise, and these are followed later by hemorrhagic tendencies. With the aforementioned methods of administration the prothrombin time can be expected to remain prolonged from seven to ten days. When rapid anticoagulation is desired, combined administration of heparin and dicoumarin is advisable. When the two substances are used together, the heparin is given intravenously and discontinued at the end of the latent period for dicoumarin. As heparin has no effect on the prothrombin time, this period is easily ascertained.

Stats and Bullowa<sup>33</sup> noted the effect of a single dose of dicoumarin on 39 patients. The dosage varied from 400 mg for patients weighing 130 pounds (58.5 Kg) or less and 600 mg to patients weighing over 160 pounds (72 Kg). They noted a prolongation of the coagulation time and a lowering of the prothrombin index of the blood for approximately six days, beginning between twenty-four and seventy-two hours after the drug was administered. At the height of the action of the drug the coagulation time varied between sixteen and forty-two minutes, in most cases being between twenty-two and twenty-six minutes. The prothrombin index varied from 100 per cent to 10 per cent of normal.

There seems to be little doubt that dicoumarin prevents intravascular thrombi. Dale and Jacques<sup>34</sup> were among the first to demonstrate this phenomenon in dogs. In one series of dogs thrombosis was produced successfully by crushing the vein, whereas among dogs receiving dicoumarin 60 per cent were completely free of thrombi. In another series, thrombosis was prevented in a series of glass cells inserted between the carotid artery and the jugular vein. Bollman and Preston<sup>35</sup> confirmed this when they noted that glass cannulas interposed between two ends of an artery are seldom occluded by thrombi when animals have received dicoumarin. Richards and Cortell<sup>36</sup> found that dicoumarin greatly reduced the incidence and degree of thrombus formation following the intravenous injection of ethanalamine oleate.

The indications for the use of dicoumarin are similar to those of heparin. Its chief advantages over heparin are its ease of administration and its low cost. Its main disadvantage is the prolonged action after administration of the drug is discontinued. It is used therapeutically in an effort to prevent arterial and venous thrombosis. It has been used in cases of pulmonary embolism and infarction,

33 Stats, D., and Bullowa, J. G. M. Effect of Single Dose of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) upon Blood Coagulation in Humans, *Proc Soc Exper Biol & Med* 50:66 (May) 1942.

34 Dale, D. U., and Jacques, L. B. The Prevention of Experimental Thrombosis by Dicoumarin, *Canad M A J* 46:546 (June) 1942.

35 Bollman, J. L., and Preston, F. W. The Effects of Experimental Administration of Dicoumarin, *J A M A* 120:1021 (Nov 28) 1942.

preoperative and postoperative thrombophlebitis, various peripheral vascular disorders, acute coronary thrombosis and subacute bacterial endocarditis. Barker, Allen and Waugh<sup>36</sup> used it in 497 surgical cases in which vascular complications seemed likely. In only 4 cases did thrombosis or embolism develop, and in 3 of these it was difficult to secure a satisfactory increase in prothrombin time. Hemorrhage was a complication in 47 of these cases, but it was minor in 29 and moderate to severe in only 18 (fatal in only 1). Bingham, Meyer and Howard<sup>37</sup> gave dicoumarin to 105 patients and found it satisfactory and safe. They administered 10 Gm over a ninety day period to a patient with thromboangitis obliterans and obtained symptomatic improvement. Lehmann<sup>38</sup> has used it successfully in Sweden, where it is known as A P (antiprothrombin). Butsch and Stewart have also used dicoumarin extensively. In a recent article<sup>39</sup> they report administering it to 23 male patients one or two days prior to doing a hemorrhaphy. The operation was completed without complications, as excessive bleeding was not encountered and healing occurred as normally expected. The purpose of this study was to demonstrate the safety of the drug when given preoperatively, especially to patients in whom postoperative complications are anticipated. Lastly, DeBakey,<sup>40</sup> in a recent editorial, warns against overenthusiasm in the prevention of postoperative vascular accidents with anticoagulants in general, reminding his readers of the normally low incidence of these complications.

There are certain definite contraindications to the use of dicoumarin. It should not be given to patients with renal insufficiency, purpura of any type, a blood dyscrasia with a tendency to bleeding, existing prothrombin deficiency (such as may occur in jaundice due to hepatic disease or malnutrition) or, lastly, subacute bacterial endocarditis. It is needless to mention its contraindication for patients with ulcerative or open lesions or with continuous gastric drainage or persons for whom a surgical operation is contemplated during the next two weeks.

#### ARTERIOSCLEROSIS

Lake and his colleagues<sup>41</sup> report their observations on the relationship of arteriosclerosis and varicose veins to the occupational activities of employees in a large department store. Five hundred and thirty-six persons were studied who had been at a particular type of work for ten years or more. They were grouped according to age and according to the manner in which they worked, namely standing, sitting, walking or climbing stairs. All of these persons were over 40 years of age, 305 were men and 231 women. The criteria for diagnosis

36 Barker, N. W., Allen, E. V., and Waugh, J. M. The Use of Dicoumarol [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] in the Prevention of Postoperative Thrombophlebitis and Pulmonary Embolism, *Proc. Staff Meet., Mayo Clin.* **18** 102 (April 7) 1943.

37 Bingham, J. B., Meyer, O. O., and Howard, B. Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin). III. A Report on Further Clinical Observations, *Am. J. M. Sc.* **205** 587 (April) 1943.

38 Lehmann, J. Hypoprothrombinemia Produced by Methylene-Bis-(4-Hydroxycoumarin). Its Use in Thrombosis, *Lancet* **1** 318 (March 14) 1942. Hypo-Prothrombinemia Produced by 3,3'-Methylene-Bis-(4-Hydroxycoumarin) and Its Use in the Treatment of Thrombosis, *Science* **96** 345 (Oct. 9) 1942.

39 Butsch, W. L., and Stewart, J. D. Administration of Dicoumarin Compound for Prophylaxis of Postoperative Thrombosis and Embolism. A Preliminary Report, *Arch. Surg.* **45** 551 (Oct.) 1942.

40 DeBakey, M. Dicoumarin and Prophylactic Anticoagulants in Intravascular Thrombosis, *Surgery* **13** 456 (March) 1943.

41 Lake, M., Pratt, G. H., and Wright, I. S. Arteriosclerosis and Varicose Veins, *J. A. M. A.* **119** 696 (June 27) 1942.

were a history of intermittent claudication, finding of rubor on dependency and pallor on elevation, absence of pulse, low oscillometric readings after release of any abnormal spasm, and evidence of arteriosclerosis as shown by roentgenograms. Forty-six per cent of the men and 20 per cent of the women were found to have evidence of arteriosclerosis by these criteria. In 177 arteriosclerosis was noted roentgenologically, and it was the sole evidence of arteriosclerosis in 147. The oscillometer revealed little evidence of pathologic change in the group as a whole, but it was responsible for detecting a larger percentage of arterial disease in women than in men. Statistical differences were more significant in the younger age group (40 to 49). In this group, stair climbing produced a higher incidence of arteriosclerosis than did standing, sitting or walking. Over the age of 50 little difference was noted in the occupational incidence. The use of tobacco and alcohol had no influence in the occurrence of arteriosclerosis in this series. A relationship was found to exist between the incidence of hypertension and that of arteriosclerosis of the lower extremities. Women showed a much higher incidence of varicose veins than men employed at the same occupation. This difference held true even when the factor of pregnancy was removed from the data. Women who had been pregnant showed a higher occurrence of varicose veins than women who had never been pregnant. Varicose veins were common in this series, being noted in 40.7 per cent of men and 73.2 per cent of women. Women who stood or walked showed a higher incidence of varicose veins than those who sat at their work. This was not noted in men. It is interesting that the incidence of arteriosclerosis of the leg arteries in men was higher in those with varicose veins, but this could not be statistically established for women.

Sappington and Fisher<sup>42</sup> report on the vascular lesions of 44 amputated gangrenous legs. The specimens were obtained from patients with arteriosclerosis obliterans. The gross study revealed an extraordinary amount of arterial occlusion, averaging 44 per cent of the entire length of the anterior tibial, posterior tibial and peroneal arteries. The average number of vessels occluded per case was two and three-tenths. The occluding lesions apparently represented various stages and regressions of organizing obstructive clots. Atheroma did not appear to be a participating feature, as vessels with the highest incidence of atheroma exhibited the lowest percentage of occlusions while those with the highest incidence of closure presented the least degree of atheromatous development. Calcification was found to be the outstanding lesion in the media. It was demonstrated in 100 per cent of 38 cases roentgenologically and in 98 per cent of 44 cases microscopically. Bone formation in the media of the peripheral arteries was found in 70 per cent of the cases. The authors expressed the opinion, on the basis of their studies, that the attempt at bone formation in a large part precedes and does not follow calcareous deposition in the media.

Dauber and Katz<sup>43</sup> were able to produce atheromatous vascular lesions in chicks by feeding the birds an adequate diet plus 2.5 to 5 per cent of cholesterol in cottonseed oil. Atheromatosis developed rather rapidly, usually beginning on the forty-second day. In this study a group of 24 cockerels 10 days old were studied, of which half were used as controls. In none of the latter group did vascular lesions develop. In 7 of the 12 cholesterol-fed birds atheromatous deposits developed in the aorta. Of these 7 chicks, 3 had intimal atheromatous lesions in the coronary

42 Sappington, S. W., and Fisher, H. R. Arteriosclerosis Obliterans, *Arch Path* **34** 989 (Dec) 1942.

43 Dauber, D. V., and Katz, L. N. Experimental Cholesterol Atheromatosis in an Omnivorous Animal, the Chick *Arch Path* **34** 937 (Dec) 1942.

arteries with resultant narrowing of the lumens of the vessels. In 2 of the 7, similar changes were noted in the splenic arteries. Unfortunately, only a small number of chicks were studied, but it is significant that the pathologic changes which were produced resembled those found in older chickens. It also lends support to those investigators who experimentally produced atheroma in rabbits and other animals with cholesterol.

Hueper<sup>44</sup> has continued his studies on the relationship between physicochemical colloidal disturbances of the plasma and the development of vascular atheromatosis and organic thesaurosis. In this study the colloidal solutions of pectin, a macromolecular carbohydrate, were injected intravenously into rabbits and dogs and the effects on the blood and the internal organs were noted. The solutions were either freshly prepared or autoclaved. The immediate effects produced on the blood by either type were a colloidoclastic leukopenia, acceleration of erythrocytic sedimentation and a moderate shortening of clotting time. When the freshly prepared solutions of pectin were injected into the animals, not only did a marked foam cell storage phenomenon develop in the spleen, kidneys and bone marrow, but a foam cell atheromatosis of various arteries was also noted. Older vascular lesions of this origin are characterized by hyaline intimal thickening with or without calcification and by hyaline necrosis and calcification in the media underneath. When the autoclaved pectin solutions were injected only minor changes were noted in the previously mentioned organs. The author explains this difference by the fact that heat will markedly depolymerize pectin solutions and will thereby destroy much of their macromolecular characteristics and original physicochemical properties.

Schlossmann<sup>45</sup> demonstrated that the fibrinoid material within arteriosclerotic aortas and peripheral vessels of the lower extremities was not a true serum fibrin. This was done by subjecting the material to tryptic digestion. He also presents evidence to show that the fibrinoid substance in these vessels was partially necrotic collagen.

#### THROMBOANGIITIS OBLITERANS

The dynamics of blood flow in 7 patients with thromboangitis obliterans was studied by Landowne<sup>46</sup>. Measurements were made by the plethysmographic method. The resting blood flow in the horizontal position in the feet of these patients was found to be within normal limits, but the maximal volume flow of blood consequent to certain dilating procedures was found to be less than that observed in normal persons. These conclusions were drawn from the observation that after the release of arterial occlusion in the thigh an initial decrease in blood flow was noted and could not be prevented by local heat or by sympathetic ganglionectomy. Although there was no evidence to indicate that the dilating procedures which were used did not produce dilatation of the small vessels, the author considers the possibility that these procedures may evoke abnormal responses in this disease, both qualitatively and quantitatively. The initial decrease in blood flow consequent to release of arterial occlusion may be caused by the factor just mentioned, by a peripheral vasoconstrictor effect of ischemia or, most likely, by a local constrictive response of the major vessels. Since the last two factors may be active in the normal subject, this constrictive response need not of necessity be caused by thromboangitis obliterans, but at least it becomes manifest in this disease.

44 Hueper, W. C. Experimental Studies in Cardiovascular Pathology. V. Pectin Atheromatosis and Thesaurosis in Rabbits and in Dogs, *Arch Path* **34** 883 (Nov.) 1942.

45 Schlossmann, N. C. Fibrinoid Necrosis in Arteriosclerosis, *Arch Path* **34** 365 (Aug.) 1942.

46 Landowne, M. Dynamics of Blood Flow in Thromboangitis Obliterans, *Am Heart J* **24** 50 (July) 1942.

Jahsman and Durham<sup>47</sup> caution the physicians examining young men of draft age to be on the alert for thromboangitis obliterans, especially if men complain of symptoms referable to the circulation. In seven months the authors encountered 7 such persons. One foot or leg was invariably more involved than the other. In some cases the symptoms were only in one digit. None of the subjects showed complete occlusion of the larger arteries.

Mills<sup>48</sup> reports an interesting case history of a man 37 years of age who complained of aching and numbness in the left calf on walking. On physical examination he was found to have occlusive vascular disease in the left leg. Prior to this illness the patient had used a pneumatic hammer in drilling rock and was in the habit of pressing the hammer down with his left foot. The leg was subsequently amputated, and the author received the report that the pathologic picture was compatible with thromboangitis obliterans.

#### GLOMUS TUMORS

Glomus tumors are reported by Loeb,<sup>49</sup> Scully<sup>50</sup> and Ottley.<sup>51</sup> No new ideas are presented.

#### PERIARTERITIS NODOSA

Very little has been added to the knowledge of periarteritis nodosa during the past year, excepting some additional evidence of the role of hypersensitivity in its causation, presented by Rich.<sup>52</sup> Additional cases are reported by ten groups of authors, but they will not be mentioned.

Krupp<sup>53</sup> uses the term "visceral angitis" to designate the group of disorders featured by peculiar lesions of small arteries, namely periarteritis nodosa, lupus erythematosus disseminata, Libman-Sacks disease and the syndromes described by Friedberg and Gross. He studied a series of 21 cases of this type, with special emphasis on quantitative studies of the urinary sediment by the method of Addis. In 7 cases no specific change in urinary sediment was discovered, but in 14 cases a singular picture of the sediment was observed. The uniqueness of this picture lies in the presence of red blood cells, red cell casts, oval fat bodies, fatty casts, broad casts and abnormal quantities of protein in the same specimen of urine. The author differentiates the urinary picture from glomerulonephritis and other renal disorders, considering the unusual sediment to be of diagnostic value in doubtful cases of the disorders just mentioned.

#### THROMBOPHLEBITIS

A fatal case of thrombophlebitis migrans is reported by Birnberg and Hansen.<sup>54</sup> The disease developed in a 14 year old boy who ultimately died of mesenteric thrombosis. Treatment with heparin was not successful. Bacteriologic studies gave

47 Jahsman, W. E., and Durham, R. H. Recognition of Incipient Thromboangitis Obliterans in Young Draftees, *Ann Int Med* **18** 164 (Feb) 1943.

48 Mills, J. H. Pneumatic Hammer Disease in Unusual Location, *Northwest Med* **41** 282 (Aug) 1942.

49 Loeb, M. J. Glomus Tumor. Report of a Case, *J Florida M A* **29** 372 (Feb) 1943.

50 Scully, J. C. Glomus Tumor, or Glomangioma, *J Michigan M Soc* **42** 118 (Feb) 1943.

51 Ottley, C. M. Glomus Tumor, *Brit J Surg* **29** 387 (April) 1942.

52 Rich, A. R. Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa, *Bull Johns Hopkins Hosp* **71** 375 (Dec) 1942.

53 Krupp, M. A. Urinary Sediment in Visceral Angitis (Periarteritis Nodosa, Lupus Erythematosus, Libman-Sacks "Disease"), *Arch Int Med* **71** 54 (Jan) 1943.

54 Birnberg, V. J., and Hansen, A. E. Thrombophlebitis Migrans, *J Pediat* **21** 775 (Dec) 1942.



no clue to the underlying cause. An allergic phenomenon was suggestive when the microscopic study revealed an eosinophilic inflammation and swelling of the intima of an involved vein.

Hirschboeck and Coffey<sup>55</sup> studied 10 patients who had pulmonary emboli. They considered not only the hemodynamic factors, and local trauma to tissues and blood vessels as etiologic agents in the development of phlebothrombosis and pulmonary emboli, but also anemia and elevation of blood fibrinogen and platelet levels as of equal importance. These factors working together result in a rapid and powerful clot retraction. The strength and rapidity of clot retraction are perhaps responsible for the loosening of thrombi from vessel walls and explain the coincidence of short clot retraction times with the occurrence of pulmonary embolism. Small amounts of heparin greatly prolong the clot retraction time, and the authors believe that heparin should be used prophylactically for patients with short clot retraction times to reduce the incidence of pulmonary embolism.

Maynard and Hollinger<sup>56</sup> studied the platelet counts of 20 patients with vascular disorders of the lower extremities. The majority of these patients had unilateral edema secondary to a venous disorder, ulcer, Schamberg's disease or some other type of dermatitis. The platelet counts were usually lower in the blood of the affected extremity than in that from the opposite extremity or the lobe of an ear. As the local diminution in platelets often parallels the local clinical conditions, in the authors' opinion this laboratory procedure is of therapeutic and prognostic significance. Unfortunately the platelet counts were so variable that one questions the accuracy of the procedure.

#### VASOSPASTIC DISORDERS

Linenthal<sup>57</sup> reports 2 additional cases of pulmonary fibrosis associated with Raynaud's disease. One patient, under observation, showed pulmonary fibrosis by roentgenograms and studies of the pulmonary dynamics. The other, at postmortem examination, showed extensive pulmonary fibrosis, with changes in the small vessels of the lungs that were consistent with the vascular changes found in the small digital arteries in advanced stages of Raynaud's disease.

Three interesting cases of interstitial calcinosis circumscripta associated with scleroderma and Raynaud's disease were reported by Bercow and Poppel<sup>58</sup>. The changes were demonstrated by interesting roentgenograms.

The important roentgen features of scleroderma and acrosclerosis are also presented by Jackman<sup>59</sup>. These include calcinosis, pulmonary fibrosis and esophageal stenosis. The last two conditions are questionable. Jackman discusses scleroderma, stressing the generalized aspect of the disease.

#### PALMAR ERYTHEMA

Bean<sup>60</sup> reports his observations on 11 additional cases of palmar erythema and cutaneous vascular "spiders." In all of these cases there was a primary hepatic

55 Hirschboeck, J. S., and Coffey, W. L., Jr. Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, *Am J M Sc* **205** 727 (May) 1943.

56 Maynard, M. T. R. Thrombocyte Deficit. The Behavior of the Blood Platelets in Diseases of Vascular Stasis of the Extremities, *J A M A* **121** 1194 (April 10) 1943.

57 Linenthal, H. Observations Concerning Pulmonary Fibrosis in Raynaud's Disease, *New England J Med* **227** 433 (Sept 17) 1942.

58 Bercow, C., and Poppel, M. H. Interstitial Calcinosis Circumscripta Associated with Scleroderma and Raynaud's Disease, *Radiology* **39** 96 (July) 1942.

59 Jackman, J. Roentgen Features of Scleroderma and Acrosclerosis, *Radiology* **40** 163 (Feb) 1943.

60 Bean, W. B. Acquired Palmar Erythema and Cutaneous Vascular "Spiders," *Am Heart J* **25** 463 (April) 1943.



or pulmonary disease. In none of them was a familial history of palmar erythema obtained. Although the author has insufficient data to support his hypothesis, he is of the opinion that these localized vascular disturbances result from an abnormality in circulating estrogenic substances and other 17-keto steroids. Lofgren's observations<sup>61</sup> lend some support to this theory. He noted a palmar erythema in 3 pregnant women which promptly disappeared after delivery. In 1 patient's case an attempt was made to duplicate the condition about four months after delivery with large doses of estrogen. Although a slight flushing of the hands developed, it was not as striking as that noted while the patient was pregnant. Trostler<sup>62</sup> has come to a different conclusion on palmar erythema. He noted it in 22 cases of pulmonary tuberculosis and in 1 case of nontuberculous empyema. The erythema was found to consist of dilated vessels, and Trostler considers it secondary to circulating toxins, basing his conclusions on previous experimental work in which capillary dilatation was produced in laboratory animals with various bacterial toxins.

#### GANGRENE

Riordan and his colleagues<sup>63</sup> cite 3 cases of pellagra, all with unusual affected areas. Of interest in this review is the case in which local gangrene of the right great toe developed on the basis of a pellagrous dermatitis. The toe was amputated, and the other cutaneous manifestations responded to nicotinic acid.

#### TREATMENT

The treatment of certain vascular disorders is gradually undergoing revolutionary changes. The use of cold rather than heat has been found to be of value in the treatment of frostbite and immersion foot, and it appears likely that it may play a more prominent role in the therapy of other organic peripheral vascular disorders in the future. Bigelow,<sup>64</sup> in an excellent survey and discussion of the literature on the physiology and treatment of frostbite, expresses the belief that one should not neglect the specific therapy already shown to be useful by previous investigators. His conclusions were drawn from a review of the literature and not from clinical study. Many of the methods referred to by Bigelow are losing their popularity, especially in the treatment of occlusive vascular diseases.

Greene<sup>65</sup> has continued to advocate the use of cold in the treatment of frostbite, immersion foot and trench foot. He has designed a refrigerator for the treatment of these conditions but has not been able to give it a clinical trial. Like others, Greene considers that frostbite and immersion foot differ only in degree of exposure. In the former, capillary damage is so severe that destruction of tissue is inevitable and no amount of therapy will restore the necrotic element. The remaining viable tissue usually responds to a cool environment. In immersion foot and trench foot, the tissues are merely in a "state of chilling," and, although the capillaries are affected, reversible changes occur and healing can be expected.

Reports on successful treatment of peripheral vascular disease with endocrine products continue to make their appearance in the literature. These studies have

61 Lofgren, R. C. Erythema of the Palms Associated with Pregnancy, *Arch. Dermat. & Syph.* **46**: 502 (Oct.) 1942.

62 Trostler, L. S. Erythema of the Extremities in Tuberculosis, *Am. Rev. Tuberc.* **47**: 168 (Feb.) 1943.

63 Riordan, T. J., Gellis, S., and Rubinowitz, A. M. Unusual Sites of Lesions in Pellagra: Gangrene of the Toe in One Case, *Arch. Dermat. & Syph.* **46**: 661 (Nov.) 1942.

64 Bigelow, W. G. The Modern Conception and Treatment of Frostbite, *Canad. M. A. J.* **47**: 529 (Dec.) 1942.

65 Greene, R. Cold in the Treatment of Damage Due to Cold, *Lancet* **2**: 695 (Dec. 12) 1942.

in general been poorly controlled. Periods of treatment have been of long duration, and objective evidence of improvement, with or without the aid of the various mechanical devices, has been meager. Subjectively, the patients usually feel better. Walker,<sup>66</sup> in a recent article on the effect of sex hormones in the treatment of various vascular disorders, included 14 patients with organic peripheral vascular diseases. These patients received androgenic and estrogenic substances. In this group 8 patients showed marked improvement, 2 responded fairly well and 4 were not benefited. In 2 patients, with characteristic thromboangitis obliterans, the results were unusually good. Beaser and Massell<sup>67</sup> attacked the problem more scientifically. They were able to evaluate therapeutic results by measuring the patient's ability to walk on a level surface at a given rate until claudication developed. Using this test, they found that testosterone propionate in doses up to 150 mg a week did not prevent intermittent claudication in the lower limbs of 6 patients with occlusive vascular disease.

Sirota<sup>68</sup> used desoxycorticosterone acetate in the treatment of thromboangitis obliterans and arteriosclerosis obliterans. This form of therapy was used because of the possibility that the adrenal cortex hormone might change salt metabolism internally and produce an effect similar to that of the intravenous administration of hypertonic salt solution. It is also claimed by many investigators that both of these preparations will increase the volume and lower the viscosity of the blood. Twenty cases were studied, and the oscillometric index, surface temperature and subjective improvement were used as criteria of cure. The author considered the results encouraging. From a study of his cases, however, this conclusion does not seem justified. Some patients were objectively better but subjectively worse, and vice versa. Improvement was certainly less than that reported with most of the established methods of treatment now available.

Fatherree and Hurst<sup>69</sup> studied the effect of an insulin-free, deproteinized pancreatic extract on 15 patients suffering from intermittent claudication. Nine of these patients suffered from thromboangitis obliterans. Injections of 3 to 5 cc were given on alternate days, excepting to 1 patient, who received the solutions daily. After an injection the authors were unable to ascertain a remarkable change in the blood pressure, pulse rate or digital cutaneous temperature. Of the 9 patients with thromboangitis obliterans, 7 were improved clinically and 2 were unimproved, as indicated by the claudication tests performed. Of the 6 patients with arteriosclerosis obliterans, none had an increase in claudication time. The authors finally concluded that the substance must be of value for some patients with intermittent claudication, but they were unable to predict which patient would benefit without a clinical trial.

Gorham and Climenko<sup>70</sup> made several laboratory and clinical studies on a new insulin-free, histamine-free pancreatic tissue extract. Surface temperature and

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66 Walker, T. C. Use of Testosterone Propionate and Estrogenic Substance in Treatment of Essential Hypertension, Angina Pectoris and Peripheral Vascular Disease, *J Clin Endocrinol* **2** 560 (Sept.) 1942.

67 Beaser, S. B., and Massell, T. B. Therapeutic Evaluation of Testosterone in Peripheral Vascular Disease, *New England J Med* **227** 43 (July 9) 1942.

68 Sirota, H. H. Value of Desoxycorticosterone Acetate in the Treatment of Peripheral Vascular Disease, *J Clin Endocrinol* **3** 141 (March) 1943.

69 Fatherree, T. J., and Hurst, C. Intermittent Claudication. Its Treatment with an Insulin Free, Deproteinized Pancreatic Extract (Depropanex), *Ann Int Med* **17** 325 (Aug) 1942.

70 Gorham, L. W., and Climenko, D. R. The Role of Insulin-Free, Histamine-Free Pancreatic Tissue Extract in the Treatment of Peripheral Arterial Disease, *Am Heart J* **25** 486 (April) 1943.

plethysmographic studies were performed on dogs after intravenous injections of this substance. A transitory fall in blood pressure was first noted, followed by evidence of vasodilatation lasting as long as fifty minutes. When the extract was administered intramuscularly, very little effect on blood pressure was noted, but there was some evidence of peripheral vasodilatation. In tests on an isolated smooth muscle in oxygenated Ringer-Locke solution relaxation of the muscle was also noted on the addition of this pancreatic tissue extract. The preparation was then injected intramuscularly into 16 normal persons. A rise in cutaneous temperature and an increase in arm volume were noted in all the subjects studied. When the opposite hand was placed in cold water for thirty seconds, far less vasoconstriction was noted after the tissue extract was used than in its absence. The substance was then injected into persons suffering from various types of peripheral vascular disorders, mainly vasospastic in origin. Similar results were obtained in almost all of them. Clinically 8 received complete symptomatic relief and 4 others received only partial relief.

Uttal<sup>71</sup> reports his impressions of Soap Lake (Washington) as a spa for the treatment of thromboangitis obliterans. It differs little from that of other investigators who have studied this form of treatment. Uttal concludes that the Soap Lake water baths have neither a beneficial nor a harmful effect on the circulation in thromboangitis obliterans. The only beneficial effect possible is due to the vasodilatation resulting from the temperature of the water (100 F). Externally Soap Lake water causes second degree burns of the skin if applied in full concentration for too long a time. Internally the water causes a hemorrhagic gastroenteritis if taken by mouth in doses over the amount necessary to produce a mild laxative or purgative effect. The climatology and open outdoor life are beneficial to patients with this disease, and it is inexpensive to live in the town of Soap Lake. Uttal finally concludes that these factors definitely helped the patients psychologically, but in no other manner.

The successful management of 30 patients with night cramps is reported by Gootnick.<sup>72</sup> These patients were all veterans of World War I and were in the fourth or fifth decade of life. They suffered from various diseases, mainly arthritic. Evidence of peripheral vascular insufficiency could not be found. Gootnick is of the opinion that the pain was due to a lasting tetanic contraction of a muscle group secondary to a reflex stimulation from a neighboring focus of irritation. This focus could well be an arthritic joint, sciatic neuritis, a traumatic residuum or some other neighboring diseased area. In addition, muscles are more likely to be overstretched while a person is lying down, which results in a tendency to recoil into spasm. Blood calcium and phosphorus were found to be within the normal limits. Twenty-eight of the patients were afforded immediate relief after an evening dose of 3 grains (0.19 Gm.) of quinine sulfate. The other 2 patients received only partial alleviation. After administration of the drug was discontinued, 6 had an immediate recurrence and 10 had a recurrence within three days. By resuming use of the drug relief was again obtained.

An excellent review on the effects of radiation on the cardiovascular system has been compiled by Warren.<sup>73</sup> In this review he covers the literature on the effect of radiation on the normal heart and blood vessels.

71 Uttal, J. Soap Lake Water for Treatment of Thromboangitis Obliterans, *Northwest Med* **42** 99 (April) 1943.

72 Gootnick, A. Night Cramps and Quinine, *Arch Int Med* **71** 555 (April) 1943.

73 Warren, S. Effects of Radiation on Normal Tissues. VI Effects of Radiation on the Cardiovascular System, *Arch Path* **34** 1070 (Dec.) 1942.

Linton <sup>74</sup> was successful in preventing gangrene in a woman 58 years of age in whom the arterial blood supply to the left leg was interrupted by ligation of the hypogastric artery and occlusion of the external iliac artery secondary to trauma. Adequate arterial circulation was reestablished by means of intermittent venous occlusion. Long periods of occlusion and short periods of release were used.

Schaefer and Sanders <sup>75</sup> describe a case of temporal arteritis which responded to the oscillating bed when other methods for the relief of pain had failed.

A case of periarteritis nodosa apparently cured with sulfapyridine is reported by Goldman and his colleagues <sup>76</sup>.

By the local application of blood or concentrated plasma, Naide <sup>77</sup> was able to relieve pain quickly, reduce the inflammatory reaction and heal 9 of 15 chronic ulcers of the leg that had resisted previous treatment by other methods. Ten of the ulcers were on an ischemic basis due to arteriosclerosis or thromboangitis obliterans, and the remaining 5 were of varicose origin. Although the mechanism of action is unknown, the question arises as to whether the applied blood supplies nutrition or whether by its sealing the ulcers with a crust of blood a more rapid healing process is initiated.

#### ARTERIAL HYPERTENSION

While the problem of essential hypertension is far from solution, a good deal has been done during the last year to clarify the subject and to erase earlier misconceptions in regard to its pathogenesis. Scott <sup>78</sup> still maintains that arteriosclerosis and atherosclerosis of the renal vessels constitute the essential pathologic defect which is responsible for the development of hypertension. He states that there is no evidence that disease of either the central nervous system or the vegetative nervous system may be the cause of this disorder. He appreciates the fact that there are other causes of hypertension than diseases of the kidney, and he emphasizes that an elevation of systolic pressure such as is usually found in elderly people may be persistently well above the normal without increasing the elevation of the diastolic pressure. This, of course, is essentially an atherosclerotic disease of the large elastic-coated blood vessels. He still maintains that the phenomenon of hypertension as reproduced in animals in which the main renal arteries are constricted is the exact counterpart of human benign essential hypertension, and he reminds the reader that even the clinical picture of malignant hypertension has been produced in animals by further narrowing of the renal arteries. He suggests also that the failure to find evidence of renal arteriosclerosis in many instances of human hypertension may well be due to the fact that sclerotic narrowing or other obstruction to vessels proximal to the kidneys is the essential factor. According to his conception, arteriosclerosis in one form or another, and in one location or another, is the primary disease of which hypertension is the manifestation. This process when affecting the vascular system of the kidneys excites the humoral mechanism which produces widespread vasoconstriction, and thus causes hypertension. Whether this is of the benign or the malignant type depends on the severity of the vascular lesion in the kidney.

<sup>74</sup> Linton, R. R. Treatment of Acute Arterial Occlusion by Means of Intermittent Venous Occlusion. Report of a Case, *Arch Surg* **46** 395 (March) 1943.

<sup>75</sup> Schaefer, C. L., and Sanders, C. E. Temporal Arteritis, *Am Heart J* **24** 410 (Sept) 1942.

<sup>76</sup> Goldman, B. A., Dickens, K. L., and Schenken, J. R. Apparent Cure of Periarteritis Nodosa with Sulfapyridine. Report of a Case, *Am J M Sc* **204** 443 (Sept) 1942.

<sup>77</sup> Naide, M. Treatment of Leg Ulcers with Blood and Concentrated Plasma, *Am J M Sc* **205** 489 (April) 1943.

<sup>78</sup> Scott, R. W. Arterial Hypertension, *J A M A* **120** 1 (Sept 5) 1942.

Schroeder<sup>79</sup> amplifies this view and states that arterial hypertension is characterized by increased peripheral resistance owing to the presence of circulating pressor substances in the blood. These substances are released by the ischemic kidneys. They cause changes not only in the arterioles but in the hemodynamics of the kidneys, leading to permanent arteriolar change. His views differ from those of Scott in that he believes that functional spasmodic constriction of the arterioles by nervous or hormonal influence initiates the vicious circle which subsequently leads to organic changes in renal vessels. When some organic renal circulatory impairment is already present, hypertension may result from even a slightly intermittent increase in renal vasoconstrictor tone, whereas when the kidneys are entirely normal such activity perhaps induced through activity of the sympathetic nervous system may have no influence in affecting a rise in blood pressure. However, if such an increase in vasomotor activity occurs repeatedly and frequently, it may be sufficient in intensity to initiate a sequence of events which leads to the development of essential hypertension.

If the functional element acts alone the course of the disease is likely to be prolonged. If there is an element of progressive structural damage and the functional one continues to exert an added influence, the course of the disease becomes more rapid and renal insufficiency may appear early. If both functional and structural elements progress rapidly, malignant hypertension is the result.

Page's<sup>80</sup> views stress the hormonal character of the pathogenesis of hypertension resulting from impairment of the blood flow through the kidney. He distinctly recognizes other types of increased blood pressure and is inclined to believe that functional vasomotor or neurogenic factors may initiate the renal ischemia which results in the release from the kidneys of the vasopressor substances responsible for subsequent rises in blood pressure. In this paper, he reviews particularly his own work and amplifies the evidence he has obtained in this work for these views in regard to the pathogenesis of hypertension. They are not new and have been reviewed before. It is interesting to note, however, that he has found in a study of the cardiodynamic effects of angiotonin that they are practically identical to those observed in primary vascular hypertension as measured by the ballistocardiograph. The similarity of the tracings obtained on persons with hypertension and on persons whose blood pressure was normal but who were made hypertensive as a result of the administration of angiotonin are striking in their similarity. He emphasizes the fact that the heart is a part of the vascular mechanism and therefore may be expected to respond in much the same way that other parts of the vascular system react to pressor substances. His paper is simple and gives an easily understandable explanation of the essential mechanisms involved in the production of hypertension according to this theory.

Simonds<sup>81</sup> discusses the renal pathologic changes in hypertension and their clinical interpretation. He states that arteriosclerosis with narrowing of the lumens of the afferent arterioles of the glomeruli is the pathologic equivalent of hypertension of long duration. In the first stage he concedes that there is probably a vasoconstriction involving these vessels which is not demonstrable as a structural change. He points out in this connection that the kidneys have both vasocon-

79 Schroeder, H. A. Essential Hypertension. A Conception of Its Mechanism, *Am J M Sc* **204** 734 (Nov) 1942.

80 Page, I. H. Studies on the Mechanisms of Arterial Hypertension, *J A M A* **120** 757 (Nov 7) 1942.

81 Simonds, J. P. Renal Pathogenic Changes in Hypertension and Glomerulonephritis. Clinical Interpretation, *J A M A* **120** 89 (Sept 12) 1942.

strictor and vasodilator fibers. While there is little actual evidence that these have an active role in the control of renal function, the fact that there is a structural basis for sympathetic renal activity leads to the belief that it must become effective when the proper stimulus is applied. He also supports the theory of the vicious circle in hypertension. He states that "as long as the kidneys produce renin they remain ischemic, and as long as they remain ischemic, they continue to produce renin." Vasoconstrictor impulses of any type, regardless of their origin, may initiate this vicious circle. In the second and third stages arteriosclerosis is not infrequent in many widespread locations in the body, but it is only in the kidneys that such changes have any constant association with hypertension. In the second stage, hypertrophy of the muscle coats and hyperplasia of the elastic laminae of the afferent arterioles are characteristic. In the third stage, the wall of the arterioles become transformed into hyaline tubes with narrowed lumens. In the two earlier stages the vessels are still capable of response to vasomotor stimuli, while in the final or hyaline stage such a response is no longer possible.

Chasis and Redish<sup>82</sup> have continued their important work on the function of the kidneys in hypertensive subjects and on renal blood flow. They believe that impairment of the renal parenchyma occurs early in hypertensive subjects and then proceeds in a parallel manner in the two kidneys. Apparently it does not follow the same pace in any two cases, but the decrease in blood flow in the two kidneys is practically the same. They failed to find a single instance of unilateral ischemia in 21 subjects with hypertension whom they had selected at random.

They also conclude that absolute reduction in renal blood flow in one or both kidneys as measured by the diodast clearance does not necessarily indicate that renal ischemia is present. They state that such a conclusion can be drawn only if the blood flow for each unit of tubular excretory tissue can be evaluated.

They were unable to find any alteration in the patterns of the ureteropyelograms made on this group of patients. They further warn that excretory tests which compare the functions of the two kidneys must be evaluated with caution, because any variation in the quantity of urinary flow from these kidneys of itself may account for variations in the appearance time and relative concentration of the dye and even in the appearance of the shadows noted in excretory pyelography.

Castleman and Smithwick<sup>83</sup> studied the biopsy specimens obtained from the kidneys of 100 patients in the course of splanchnic resection for hypertension. The most striking result of these observations was finding such a high proportion of the renal biopsies in which there was no, or only minimal, degenerative disease in the vascular structures. Medial hypertrophy was present in only 40 per cent of the cases. Peripheral arteriosclerosis was present in only 7 per cent of the grade I group, whereas 60 per cent was noted with grades III and IV. Elevation of blood pressure precedes the development of structural disease of the blood vessels within the kidneys, as well as of the peripheral arterioles. It is therefore reasonable to believe that some vasoconstrictor mechanism carries on the ischemic process until renal vascular disease develops. When this has become established hypertension becomes more severe, and the blood pressures of persons in that stage become fixed at higher levels.

82 Chasis, H., and Redish, J. Function of the Separate Kidneys in Hypertensive Subjects, *Arch Int Med* **70**:738 (Nov) 1942.

83 Castleman, B., and Smithwick, R. H. The Relation of Vascular Disease to the Hypertensive State Based on a Study of Renal Biopsy from One Hundred Hypertensive Patients, *J A M A* **121** 1256 (April 17) 1943.

Such results in the study of structural defects could well be expected under these conditions, for the patients in this group were no doubt selected for splanchnic section because little or no evidence of organic vascular disease could be detected.

It is also interesting to note that in this group adrenal tumors were found in 7 patients. The presence of the tumors was not suspected.

That hypertension is an important factor in the development of arteriosclerosis is indicated by the observations of Lake and his co-workers,<sup>84</sup> who found that there was a much higher incidence of this disease among persons with hypertension than in those without.

The factor of age is also emphasized by Russek<sup>85</sup> in discussion of the relationship of this factor to increased blood pressure. He found in a statistical analysis of blood pressure levels of 1,000 male subjects between the ages of 60 and 95 that there was an evident increase in the average systolic and pulse pressures with age. The diastolic pressure showed little variation after the age of 65. The incidence of normal blood pressure, of 150 systolic and 95 diastolic or less, decreased with age. Less than one half of the readings fell in this group. The incidence of normal systolic pressure increased with age, whereas that of normal diastolic pressure showed a tendency to fall with age. Arteriosclerosis apparently increased the incidence of systolic hypertension only. It is interesting to note that the life expectancy of the persons with systolic hypertension is of the same order as for those with normal pressure. Diastolic hypertension, on the other hand, carries a much less favorable prognosis. Diastolic hypertension was found in less than one-quarter of the entire group.

Howell<sup>86</sup> made essentially similar observations. He states that pronounced arteriosclerosis in the absence of systolic elevation in blood pressure was usually associated with poor physical condition, and he found the systolic blood pressure elevated in more than 42 per cent of his group of subjects.

Master<sup>87</sup> and his associates made another survey on 15,000 persons of all ages. The presence of hypertension in persons over 40 is becoming increasingly important because of the fact that many more persons survive this age. They gave further attention to the normal level of blood pressure, and in their paper they consider a fairly wide variation. The diastolic pressure was taken at the fifth phase—the disappearance of tone. They found very much the same increase in systolic pressure according to age among men. A majority showed an increase of pressure beginning with the age of 60, although this often occurred as early as the age of 50. At the age of 50 there were a 50 per cent incidence of hypertension in males and a 62 per cent incidence in females. The incidence of hypertension rose with each decade of age up through the eighth, and in the case of systolic pressure only, up through the ninth. The presence of some increase in blood pressure beyond the age of 40 is so common that in a mild degree it can no longer be considered abnormal in their opinion.

Schroeder<sup>88</sup> studied 50 patients with early stages of hypertension. Thirty-five of these patients were under 30 years of age, and 15 were under 20. They apparently presented the earliest stages of the disease. Renal disease in some form was

84 Lake, M., Pratt, G. H., and Wright, I. S. Arteriosclerosis and Varicose Veins Occupational Activities and Other Factors, *J. A. M. A.* **119** 696 (June 27) 1942.

85 Russek, H. I. Blood Pressure in the Aged, *Am. Heart J.* **26** 11 (July) 1943.

86 Howell, T. H. Blood Pressure and Old Age, *Brit. Heart J.* **4** 143 (Oct) 1942.

87 Master, A. M., Marks, H. H., and Dack, S. Hypertension in People Over Forty, *J. A. M. A.* **121** 1251 (April 17) 1943.

88 Schroeder, H. A. Studies on Essential Hypertension. IV. Early Arterial Hypertension, *Am. J. M. Sc.* **204** 62 (July) 1942.



present in 74 per cent, and Schroeder believes that this incidence was not a coincidence but rather an important factor in the genesis of the elevation of blood pressure. He thinks that organic vascular and renal diseases are thus intimately associated. Eleven of these patients were found to show dysfunctions of the nervous system, and every patient had abnormal nervous tension of some type. The onset of the increase of blood pressure in some cases was definitely associated with physical or psychologic disturbances.

The familial tendency to hypertension has long been a matter of discussion. Feldt and Wenstrand<sup>89</sup> in an analysis of 4,376 insurance examinations arrived at the conclusion that the incidence of familial cardiovascular disease was very slightly greater among hypertensive persons than it was among persons with normal blood pressure.

The psychosomatic aspects of hypertension are discussed by Weiss<sup>90</sup>. He states that two emotions are frequently closely related to hypertension. These are anxiety and rage. He emphasizes the fact that rage is an emotion which has long been connected with high blood pressure. In his opinion long-continued repressed rage may manifest itself through the circulatory system by elevation in blood pressure. Hypertension is one of the commonest disorders of civilized life, and anxiety states are no less common, therefore, from the standpoint of their frequency it is not surprising that the two are present often in the same person. It is his view that repressed rage results in a psychologic conflict which produces the tension which seems to be related to increased blood pressure, and that this is chief among multiple factors that enter into the pathogenesis of the disease. He emphasizes the fact that many of the symptoms of the hypertensive patient are not necessarily due to the increase in blood pressure but are due to the other associated disorders, both functional and physical. The emotional factors are as important as the physical factors. He stresses the frequent relationship of migraine to hypertension, and he believes that many of the severe headaches associated with hypertension may be on an emotional basis rather than due to any abnormality of blood pressure. All varieties of character and neurotic disturbances occur in hypertensive persons, but inhibited aggression seems to bear the most consistent relationship to this symptom, and this may well be one of the important factors initiating the development of the vasomotor disturbances of the primary phase of the disease.

In a discussion of the prognosis of hypertension a group of workers headed by Daley<sup>91</sup> classify the disorder in five major types: renal, endocrine and vascular hypertension, hypertension due to disease of the central nervous system, and the so-called essential hypertension, of unknown origin. They consider that blood pressures above 140 systolic and 90 diastolic are definitely abnormal at any age. The actual mortality exceeds the expected in a rapidly rising ratio for both systolic and diastolic values above this level. In the early stages of hypertension variability of blood pressure is well marked, but this initial variability is gradually succeeded by fixation at higher levels. This would indicate the development of organic changes in the arterioles in the form of hypertrophy of the media and arteriosclerosis. The presence of atherosclerotic vascular changes superimposed on vasospastic diastolic hypertension is largely responsible for the mortality from this

89 Feldt, R. H., and Wenstrand, D. E. W. The Family History in Arterial Hypertension. Studies of 4,376 Insurance Examinations, *Am J M Sc* **205** 61 (Jan) 1943.

90 Weiss, E. The Psychosomatic Aspects of Hypertension, *J A M A* **120** 1081 (Dec 5) 1942.

91 Daley, R. M., Ungerleider, H. E., and Gubner, R. S. Prognosis in Hypertension, *J A M A* **121** 383 (Feb 6) 1943.



disease. Thus, the duration of the presence of hypertension is also an important factor in prognosis. Cardiac enlargement and electrocardiographic as well as roentgen studies of the heart are valuable in estimating the outlook. Among patients with symptoms resulting from hypertension a very large number showed electrocardiographic abnormalities. The status of the kidneys is also extremely important. The renal and urinary findings are usually sufficiently in evidence so that the diagnosis of malignant nephrosclerosis is at least suggested. There are many other factors to be considered in the outlook for this disease, the retinal findings are well known, the age at which hypertension develops seems to influence its course, the constitutional type of the hypertensive subject is another factor of importance. Sex is likewise a factor. While hypertension is more frequent in females, the course of the disease seems to be more benign than in males. Concurrent diseases such as diabetes constitute a factor of considerable importance in increasing the gravity of the prognosis.

Seasonal fluctuations in normal blood pressure are discussed in a paper by Paul,<sup>92</sup> who made observations on 900 healthy young men. Little variation could be established. This may be because his observations were made on a group of relatively young persons.

The effect of toxemia of pregnancy and of pregnancy on the hypertensive state has been the subject of a number of papers and both still continue to be considered of importance in this disorder.

Dexter, Weiss, Haynes and Sise<sup>93</sup> present a comprehensive review of this subject. They based their observations on 100 normal pregnant women, 100 patients with generalized edema without hypertension during pregnancy and 80 patients with hypertension during pregnancy. Several types of hypertension in pregnancy were noted. Six to 9 per cent of the normal women had either hypertension or albuminuria or both in the latter half of pregnancy but not in the first half. Twenty of 39 patients who had hypertension before pregnancy failed to have any further increase in blood pressure or albuminuria during pregnancy in spite of the fact that many of them showed generalized edema. In the remaining members of this group with hypertension preceding pregnancy, toxemia developed. The vascular syndrome which was thus superimposed on previously existing hypertension differed in no way from the preeclampsia and eclampsia which occurred in patients whose blood pressure was normal before pregnancy. A progressive rise in the blood to above the level existing before pregnancy presaged the development of toxemia of pregnancy. Elevation of blood pressure and albuminuria of themselves do not indicate that toxemia is present.

These observers regard toxemia of pregnancy as an acute vascular disease which closely resembles acute glomerulonephritis. Etiologically and pathologically the two diseases differ. The most important factors predisposing to the development of toxemia are hypertensive disease and generalized edema. Persons with low renal reserve or with hypertension in the malignant phase seem to be especially susceptible.

Permanent vascular disease seems to follow toxemia of pregnancy much more frequently in those cases in which the duration of the disorder is prolonged and, curiously, in those cases in which the toxemia is mild rather than in those in which there is eclampsia. After a toxemic pregnancy, it is usual for hypertension to disappear rapidly. In some cases it may persist for a rather long time and even

<sup>92</sup> Paul, H. Seasonal Changes in Circulatory Factors, *Arch f Kreislaufforsch* 9 164 (Oct.) 1941.

<sup>93</sup> Dexter, L., Weiss, S., Haynes, F. W., and Sise, H. S. Hypertensive Toxemia of Pregnancy. Pre-Eclampsia and Eclampsia, *J. A. M. A.* 122 145 (May 15) 1943.

then disappear permanently. It is impossible to differentiate such cases from those in which the hypertension is progressive and the condition becomes indistinguishable from other types of chronic hypertensive disease.

Tillman<sup>94</sup> comments on the difficulty of accepting the view that the eclampsia in pregnancy is the same as that in acute glomerulonephritis, even though the clinical pictures of the two disorders are similar. In the main, his conclusions are similar to those of the previous observers. Development of sudden severe hypertension during the course of pregnancy or sudden increase in blood pressure in preexisting hypertension is of the utmost significance. The ultimate outcome cannot be determined until after delivery. In many women the condition disappears at the time, in others persistent hypertension may follow, and a considerable number of the patients present themselves later in life with typical hypertensive vascular diseases.

Eastman and Whitridge<sup>95</sup> are more specific in their views in regard to a significant rise in blood pressure as an indication of impending eclampsia. They regard a rise from 110 systolic and 70 diastolic to 135 systolic and 85 diastolic in a young woman as of more significance than a rise from 135 systolic and 85 diastolic to 150 systolic and 90 diastolic in a patient of 35. They point out that in the person with hypertension each subsequent pregnancy adds its increment to its severity. Very often in such women the disease becomes progressive and pursues a malignant course. They state that chronic hypertension is superseding eclampsia as a cause of death in child bearing and that it has been responsible for 80 per cent of the toxemic deaths in their experience.

It is interesting to note that in rats previously made hypertensive by constriction of one renal artery the systolic pressure was reduced significantly during pregnancy. After delivery the pressure rose again to approximately the same level as before. This occurred if renal damage was not severe enough to impair function.<sup>96</sup>

Dalton and Nuzum<sup>97</sup> made statistical studies on patients with essential hypertension. It has been the opinion of most observers that renal function is not impaired in this disorder, but these observations would indicate otherwise. They were based on the urea clearance test and the excretion of phenolsulfonphthalein. Dalton and Nuzum state that in subjects with essential hypertension there is a significant reduction in the ability of the kidneys to concentrate urine and to excrete phenolsulfonphthalein. This reduction can be demonstrated only when the study is considered for entire groups of normal persons and of patients with hypertension. It cannot be shown when individual comparisons are made. The age of the patient and the duration of the disease seem to have little effect on renal function of either normal persons or patients with hypertension. An increase in the severity of the disease, that is, a rise in the diastolic blood pressure, is accompanied by reduction of renal function.

Studies of the adrenal glands were made by Dempsey<sup>98</sup> on patients with essential hypertension and on a group of persons with normal blood pressure. This pathologic study showed that the average weight of the adrenal glands of

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94 Tillman, A. J. B. Classification and Medical Relationships of Hypertensive Albuminuric Pregnancy, *J. A. M. A.* **120**: 587 (Oct. 24) 1942.

95 Eastman, N. J., and Whitridge, J., Jr. The Prevention of Toxemia of Pregnancy, *J. A. M. A.* **120**: 729 (Nov. 7) 1942.

96 Foa, P. P., Foa, N. L., and Peet, M. M. Effect of Pregnancy on Experimental Renal Hypertension in Rats, *Am. J. M. Sc.* **204**: 350 (Sept.) 1942.

97 Dalton, J. W., and Nuzum, F. R. Critical Statistical Analysis of Data on Renal Function in Grouped Subjects with Essential Hypertension, *Arch. Int. Med.* **70**: 948 (Dec.) 1942.

98 Dempsey, W. S. The Adrenal Cortex in Essential Hypertension, *Arch. Path.* **34**: 1031 (Dec.) 1942.

subjects with hypertension was not significantly higher than in nonhypertensive persons. Adenomatous hyperplasia of the adrenal cortex was not found in association with essential hypertension, but it occurred with considerable frequency in nonhypertensive persons. The microscopic appearance of tortuosity of the adrenal cortical cords and abnormal deposition of fine lipid droplets in the cortical cells could not be associated with the gross findings of irregularity of the cords in the adrenal cortex.

Van Bogaert and van Baarle<sup>99</sup> state that in some cases of essential hypertension there are certain signs which resemble those produced by experimental stimulation of the hypothalamus in dogs. They were able to show the presence of hypophyseal hormones in a larger than normal quantity in the body fluids, but they concluded that this does not necessarily indicate a causal connection between the hormones and increased blood pressures and that both the rise in blood pressure and these increased secretions are the result of stimulation of the encephalobulbar centers. The hypothalamus is among these.

Evans and Stewart<sup>100</sup> studied the peripheral blood flow before and after operation for adrenal pheochromocytoma. Several interesting observations are recorded. A decrease of peripheral blood flow was noted before operation. This was attributed to hyperepinephrinemia. The circulation time was shorter before operation than after. Low cutaneous temperatures and high rectal temperatures were noted before operation and were interpreted as being brought about by decreased peripheral blood flow and vasoconstriction, which result in increased heat storage. The periods of marked sweating which were observed suggested an attempt on the part of the organism to increase loss of heat from the body by the cooling effect of evaporation.

#### CLINICAL COUNTERPARTS OF EXPERIMENTAL HYPERTENSION

Aneurysm of the abdominal aorta is capable of causing renal ischemia of sufficient degree to produce hypertension of a fairly severe grade. This is indicated by a case reported by Hoffman<sup>101</sup>. The disease process in this case was a saccular aneurysm of the abdominal aorta in a Negro man aged 28. This aneurysm was in such a location that severe compression of one renal artery occurred. It was a typical clinical example of compression of the Goldblatt type. The outstanding change seen in the involved kidney was uniform and diffuse atrophy of the nephron units with marked dilatation and engorgement of the glomerular and interstitial capillaries with red cells. There was apparently little or no sclerosis of the arterioles.

Another instance of hypertension<sup>102</sup> suspected to be the result of renal ischemia is reported as a complication of a dissecting aneurysm of the abdominal aorta. The blood pressure in this case was high, and the renal function was good. An intravenous urogram showed impaired excretion by the left kidney, but a retrograde pyelogram was normal. The dissecting aneurysm at autopsy had resulted in a complete occlusion of the left renal artery, while that of the right kidney was normal. In this case, too, there was a striking absence of sclerosis or necrosis of the arterioles of the kidney.

99 van Bogaert, A., and van Baarle, F. Contributions to the Study of Arterial Hypertension in Connection with the Hypothalamohypophyseal System, *Cardiologia* 5 275, 1941.

100 Evans, W. F., and Stewart, H. J. Peripheral Blood Flow in the Case of Adrenal Pheochromocytoma Before and After Operation, *Am Heart J* 24 835 (Dec) 1942.

101 Hoffman, B. J. Renal Ischemia Produced by the Abdominal Aorta, *J. A. M. A.* 120 1028 (Nov 28) 1942.

102 Baerøe, K. Hypertension as a Result of Renal Ischemia in Dissecting Aneurysm of the Aorta, *Nord med (Norsk mag f lægevidensk)* 12 3408 (Nov 29) 1941.

That interference with blood flow through the renal arteries may be effected by so simple a lesion as torsion resulting from ptosis is shown by the case reported by Riskind and Greene<sup>103</sup> The patient had a well marked hypertension There was no demonstrable impairment of the function of either kidney Torsion of the right kidney was suggested by urography After the application of a corset by which correction of the torsion was made, the blood pressure fell, and it had remained "fairly close to normal" After removal of the support, the pressure rose again The authors do not clearly state the findings after the support was applied, but apparently the result was definite improvement

Richardson<sup>104</sup> found 25 instances of atherosclerosis of the renal arteries In 22 of them the plaques were confined to a significant part of each artery near the aorta In 2 the involvement was confined to one renal artery In 8 there was a generalized atherosclerosis In 12 atheroma was limited to the aorta, and in 5 no atheroma was discovered Among the group there were 3 cases of malignant hypertension Richardson believes that atheromatous plaques may be capable of producing renal ischemia and consequently hypertension analogous to experimental hypertension

#### EXPERIMENTAL HYPERTENSION

Abell and Page<sup>105</sup> have continued to make direct observations on the blood vessels, particularly the arterioles, in the ears of rabbits Experimental renal hypertension causes constriction in these vessels which is easy to see and which is persistent It is not great enough to restrict the flow of blood to the tissues but is sufficient to produce increased peripheral resistance This effect is produced even in the absence of nerve supply to the blood vessels, and therefore it must be due to the direct action of some substance on the vessel structures themselves New arteriovenous anastomoses are formed These observations are remarkably similar to those made when angiotonin is injected into the animal and hypertension produced in that manner

That renal blood flow can be altered by the position of the kidney and the angle of the renal artery in relation to the aorta is shown by the experimental work of Gabriele<sup>106</sup> His observations indicate that flow is reduced to a considerable degree when the angle is made relatively acute Whether this is a factor in human hypertension depends on the mobility of the kidney He considers it likely that the hypertension of pregnancy may be influenced by such a change in the position of the kidney

The arterial hypertension which occurs in hydronephrosis has been the subject of experimental study by Megibow, Katz and Rodbard<sup>107</sup> It was found that hydronephrosis produced by constriction or obstruction of the ureters of dogs resulted in elevation of blood pressure which was transient unless bilateral ureteral obstruction was complete Under this condition hypertension existed until death of the animals in uremia If the hydronephrosis was complicated by renal ischemia in one kidney the tendency to hypertension was increased The authors believe that renal

103 Riskind, L. A., and Greene, H. H. Renal Torsion and Ischemia Causing Hypertension, *J. A. M. A.* **119** 1016 (July 25) 1942

104 Richardson, G. O. Atherosclerosis of the Main Renal Artery in Essential Hypertension, *J. Path. & Bact.* **55** 33 (Jan.) 1942

105 Abell, R. G., and Page, I. H. The Effects of Renal Hypertension on the Vessels of the Ears of Rabbits, *J. Exper. Med.* **75** 673 (June) 1942

106 Gabriele, D. J. Effect of Kidney Position on Renal Blood Flow and Function, *Am. J. M. Sc.* **204** 227 (Aug.) 1942

107 Megibow, R. S., Katz, L. N., and Rodbard, S. The Mechanism of Arterial Hypertension in Experimental Hydronephrosis, *Am. J. M. Sc.* **204** 340 (Sept.) 1942

hypertension depends on the ratio of ischemic tissue to normal kidney tissue. Both factors operate in hydronephrosis, and the severity of the increase in blood pressure depends on the rapidity with which these processes develop. A compensatory increase in normal renal tissue may be the reason why the hypertension is transitory in those instances in which the obstruction to the ureter is not complete.

The renal lesions which seem to be most effective in the production of hypertension are those which interfere with the propagation of the arterial impulse through the vessels of the kidneys. These are ureteral obstruction, constricting perinephritis and inflammatory diseases. Pyelonephritis, hydronephrosis, tuberculosis and tumor are listed as common causes by White, Durkee and Mirabile<sup>108</sup>

The part that renin plays in the production of the pressor substance which is responsible for the maintenance of elevation of blood pressure is so generally accepted that further review is not needed. It is the common opinion that renin is released only by impaired renal tissue. That the intact kidney may secrete renin under certain conditions is pointed out by Huidobro and Braun-Menendez<sup>109</sup>. They found that profound lowering of blood pressure by hemorrhage or shock causes liberation of renin by the intact kidneys of anesthetized dogs. They could detect the presence of renin in the blood of such animals, but if the kidneys had previously been removed none could be demonstrated under similar conditions. Nor could renin be detected in normal dogs when they were intoxicated with potassium cyanide or when they were made to breathe an atmosphere poor in oxygen. These authors believe that the renal humoral pressor mechanism participates in the normal maintenance of arterial blood pressure. When the blood pressure decreases sufficiently, renin is released, and this, through the formation of the pressor substance helps to bring about a restoration of pressure to normal.

Weinstein and his associates<sup>110</sup> found that blood from a kidney in which the arterial blood flow and pressure had been greatly reduced possessed a greater vasoconstrictor effect and a lesser ability to neutralize angiotonin than did blood from a normal kidney.

Acute neurogenic hypertension produced by section of the moderator nerves<sup>111</sup> occurs even after both kidneys have been removed. The rise in arterial pressure occurs immediately under these conditions just as it does when the kidneys are intact in the animal. Thus it would seem that humoral pressor substances have no part in the mechanism of this type of experimental hypertension.

The rat has been found to be an animal suitable for the study of experimental hypertension, and it is being widely used for this purpose. Chronic hypertension can be produced by a variety of measures, according to Grollman and Williams<sup>112</sup>. They have found that the application of silk to the kidneys is an easy and practical procedure with relatively low operative mortality which results in permanent elevation of blood pressure.

108 White, B. V., Durkee, R. E., and Mirabile, C. Renal Hypertension. A Review of Its Status Including a Report of a Case of Hypertension Relieved After Nephrectomy, *New England J. Med.* **288** 277 (March 4) 1943.

109 Huidobro, F., and Braun-Menendez, E. The Secretion of Renin by the Intact Kidney, *Am. J. Physiol.* **137** 47 (Aug.) 1942.

110 Weinstein, H., Friedman, M., Newman, H. L. and Sugarman, I. The Vasoconstrictor and Angiotonin Neutralizing Properties of Renal Venous Plasma, *Am. Heart J.* **25** 682 (May) 1943.

111 Thomas, C. B. Experimental Hypertension from Section of the Moderator Nerves. Relationship to the Presence of Kidney Tissue, *Proc. Soc. Exper. Biol. & Med.* **48** 24 (Oct) 1941.

112 Grollman, A., and Williams, J. R., Jr. Experimental Hypertension in the Rat. *Am. J. M. Sc.* **204** 73 (July) 1942.

Similar observations have been recorded by others,<sup>113</sup> with the same conclusions. The rat apparently has a predisposition to hypertension, so that the procedure is uniformly successful. Suitable methods for determining pressure have been devised.

As a consequence of the development of these methods of study, naturally a large number of reports have appeared on the effects of various and varied substances on the blood pressure of rats. Many of these are routine experiments with the common vasodilators. It is not possible to evaluate these results on their importance,<sup>114</sup> but it seems probable that experimentation in this field of therapeutics may prove to be extremely fruitful.

#### STUDIES OF DIODRAST AND OF INULIN CLEARANCE

The opinions in regard to the significance of determinations of diodrast and of inulin clearance as measures of the effective renal blood flow and the glomerular filtration rate are not entirely in agreement even after several years of observation, particularly when these measures are applied to the kidneys of hypertensive patients. The essential difference of opinion seems to be in regard to the detection of renal ischemia.<sup>115</sup>

Findley, Edwards, Clinton and White found that a high percentage of their relatively small group of patients with hypertension had normal clearance of diodrast and normal tubular excretion. Although no proof is at hand, they are inclined to believe, as Kohlstaedt and Page<sup>116</sup> do, that the production of the pressor substance resulting from the release of renin by the kidney is not dependent necessarily on actual reduction of renal blood flow but is due to the impairment of the pulsatile type of flow, with a reduction of pulse pressure within the renal vessels.

This opinion is shared by Foà, Woods, Peet and Foà,<sup>117</sup> who based their observations on studies of diodrast and of inulin clearance before and after surgical interruption of structures of the sympathetic nervous system according to the methods of Peet. These were carried out in cases of well advanced hypertension and in others in which the hypertension was not severe. Even though there was a reduction of blood

113 Schroeder, H. A. Arterial Hypertension in Rats. I. Methods, *J. Exper. Med.* **75** 513 (May) 1942.

114 Kempf, G. F., and Page, I. H. Production of Experimental Hypertension and the Indirect Determination of Arterial Systolic Pressure in Rats, *J. Lab. & Clin. Med.* **27** 1192 (June) 1942. Duncan, G. W., and Hyman, C. M. S. Determination of Blood Pressure in Rats by Direct Observation of Blood Vessels, *ibid.* **28** 886 (April) 1943. Rath, M., and Krantz, J. C. Nitrites. X. Effect of Sodium Nitrite upon the Blood Pressure of Unanesthetized Hypertensive Rats, *Proc. Soc. Exper. Biol. & Med.* **50** 248 (June) 1942. Friedman, B., Soloway, S., Marrus, J., and Oppenheimer, B. S. Quinones as Blood Pressure Reducing Agents in Hypertensive Rats, *ibid.* **51** 195 (Oct.) 1942. Calder, R. M. Nutritional Deficiencies as a Cause of Elevated Blood Pressure in Rats, *J. Exper. Med.* **76** 1 (July) 1942. Grollman, A., and Harrison, T. R. Reduction of Blood Pressure of Hypertensive Rats by Administration of Certain Marine Oils, *Proc. Soc. Exper. Biol. & Med.* **52** 162 (March) 1943. Oster, K. A., and Sobotka, H. Antipressor Effects of Orthoquinoid Epinephrine Derivatives in Experimental Hypertension in the Rat, *J. Pharmacol. & Exper. Therap.* **78** 100 (May) 1943. Yeatham, J. H., and Drill, V. A. The Effect of Diethylstilbestrol on the Blood Pressure of Normal and Hypophysectomized Rats, *Am. J. Physiol.* **139** 17 (May) 1943.

115 Findley, T., Edwards, J. C., Clinton, E., and White, H. L. Clearance of Diodrast, Phenolsulfonphthalein, and Inulin in Hypertension and in Nephritis, *Arch. Int. Med.* **70** 935 (Dec.) 1942.

116 Kohlstaedt, K. G., and Page, I. H. Production of Renin by Constricting the Renal Artery of an Isolated Kidney Perfused with Blood, *Proc. Soc. Exper. Biol. & Med.* **43** 136 (Jan.) 1940.

117 Foà, P. P., Woods, W. W., Peet, M. M., and Foà, N. L. Effective Renal Blood Flow, Glomerular Filtration Rate and Tubular Excretory Mass in Arterial Hypertension, *Arch. Int. Med.* **71** 357 (March) 1943.

pressure which was observed for as long as twelve months after operation there was no significant change in the diodast and on inulin clearance. Some factor other than renal ischemia is suggested as the primary cause of hypertension, and these observers expressed the opinion that intra-renal pulse pressure is the probable factor. They ascribe the effect of sympathectomy in lowering blood pressure to the removal of vasomotor tone from the arterioles of the kidneys, which may thus allow a greater pulse pressure. The reduction of systemic blood pressure occurs because less renin is secreted as a result of the increased pulsation within the kidneys. The amount of vasomotor relaxation which occurs is thought to be dependent on the amount of permanent organic change which has already occurred in the vessels affected. When this is minimal and vasoconstrictor tone maximum, good results may be secured. The converse is also true, and within the possible range all gradations may be present.

This hypothesis is ingenious and interesting and exceedingly plausible. The same question presents itself which has aroused controversy before. Do the vessels of the kidney regain their tone after denervation through increased susceptibility to humoral or hormonal substances, such as epinephrine?

#### RELATION OF UROLOGIC DEFECTS TO HYPERTENSION

It has been well established that there is a relationship between hypertension and some types of urologic disease, for example, chronic atrophic pyelonephritis, probably hydronephrosis and some types of tumor. It would seem that disease of the lower part of the urinary tract is not likely to cause a rise in blood pressure unless there is also some involvement of the vascular structure of the kidney. Studies of urologic defects and case reports continue to be frequent. Wosika, Jung and Maher<sup>118</sup> made a statistical study of a large group of cases, approximately 2,000. They found that 40 per cent of the patients with hypertension also had abnormalities of the urinary tract. Twenty-seven per cent of persons who had normal blood pressure also had urologic disease. These findings became more prominent with statistical analysis, so that the authors could conclude that the patient who has hypertension is more likely to have urologic defects than is the normal person.

A study of the retrograde pyelograms of 100 persons with hypertension and 100 without was made by Shrader, Young and Page.<sup>119</sup> Some variations in the form of the pyelogram seemed to be more common in persons who had hypertension. They had renal pelves which were larger than normal and pelves which were lower in position than usual. Other abnormalities, such as intra-renal pelvis, incomplete rotation, right-angled ureteropelvic junction and bifid pelvis, were no more common than in normotensive persons. Twenty-two per cent of the patients who had defective pyelograms also had hypertension. The incidence of significant renal abnormalities in an unselected group of hypertensive patients was 19 per cent. The difference in the patterns of the pyelograms of persons with hypertension and of those without is not great enough to have any special significance.

Kahn and Laipply<sup>120</sup> found that in nearly all cases of hypertension which is persistent renal disease is bilateral. It is frequently more severe in one kidney.

118 Wosika, P. H., Jung, F. T., and Maher, C. C. Urologic Hypertension as an Entity, *Am. Heart J.* **24**: 483 (Oct.) 1942.

119 Shrader, J. C., Young, J. M., and Page, I. H. Pyelograms in Patients with Essential and Malignant Hypertension, *Am. J. M. Sc.* **205**: 505 (April) 1943.

120 Kahn, J. R., and Laipply, T. C. Frequency of Bilateral Renal Disease in Persons with Hypertension, *Am. J. M. Sc.* **203**: 807 (June) 1942.



than in the other, often to the point of complete loss of function, but the other kidney is seldom normal. One thousand cases were included in this necropsy study. In all, the final diagnosis was arterial nephrosclerosis or arteriolar nephrosclerosis or both.

Flocks'<sup>121</sup> findings in a small group of cases carefully studied are similar but show a greater incidence of hypertension, probably because the renal defects were of types more likely to produce increased pressure. All his cases were instances of congenital hydronephrosis, infected hydronephrosis or renal calculus. In 23 of this group of 38 there was a consistent elevation of arterial tension.

Ratliff and Conger<sup>122</sup> are of the opinion that when hypertension is present in a person who has unilateral renal disease nephrectomy should be done, not only to cure the renal defect but because in a small proportion of such patients the hypertension will also be relieved. In 528 patients with hypertension the incidence of actual renal disease was small, in only 32 was there definite objective evidence. Of these, 12 had chronic pyelonephritis and 5 had calculi. The other patients did not have conditions of the type with which hypertension occurs.

That unilateral pyelonephritis can produce severe hypertension is substantiated by the case of a child of 12 years reported by Wilson and Chamberlain.<sup>123</sup> Nephrectomy resulted in a restoration of blood pressure to normal in spite of the fact that the patient showed evidence of extensive general vascular disease, evidently the result of the severe hypertension.

Braasch and Wood<sup>124</sup> comment on the incidence of hypertension and perinephritis. Of a group of 70 cases, in only 3 could there have been any relationship between the renal disease and the elevation of blood pressure. This is less than one-half the average incidence of hypertension.

The relationship of chronic pyelonephritis to hypertension is emphasized by the studies of Shure,<sup>125</sup> who in 11,898 autopsies found an incidence of 44.4 per cent, as compared with 34.9 per cent in a control group selected at random. This greater incidence occurred in cases of bilateral pyelonephritis. He found that when the disease was unilateral hypertension was comparatively rare. The incidence of hypertension increased with age and was parallel to the incidence of severe renal vascular damage.

Treatment of hypertension in the past two years has held considerable promise, but this has not yet been realized. The work done with renal antipressor substances as reported in last year's review has been advanced no further, although there is still hope that some help will come in the solution of this problem from the field of experimental study. Page<sup>126</sup> states that the "treatment of hypertension is still an experiment" and that impatience may lead only to forced conclusions rather than to the actual truth.

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121 Flocks, R. H. Clinical Studies on the Relationship Between Renal Disease, Renal Function and Arterial Blood Pressure, *J. Urol.* **47**: 602 (May) 1942.

122 Ratliff, R. K., and Conger, K. B. Incidence of Renal Hypertension and of Cure by Nephrectomy, *J. Urol.* **48**: 142 (Aug.) 1942.

123 Wilson, C. L., and Chamberlain, C. T. Unilateral Renal Ischemia with Hypertension. Case Report, *J. Urol.* **47**: 421 (April) 1942.

124 Braasch, W. F., and Wood, W. W., Jr. Clinical Perinephritis and Its Effect on Blood Pressure, *J. Urol.* **48**: 343 (Oct.) 1942.

125 Shure, N. M. Pyelonephritis and Hypertension, *Arch. Int. Med.* **70**: 284 (Aug.) 1942.

126 Page, I. H. Medical Aspects of High Blood Pressure, *J. Michigan M. Soc.* **42**: 294 (April) 1943.



Wakerlin and his associates<sup>127</sup> have continued their observations on the effect of hog renin in the treatment of experimental hypertension. They were able to prevent the development of experimental hypertension in dogs by daily intramuscular injections of partially purified hog renin for three months before and after the operation. Other similar organic preparations had no such effect. They were also able by daily injections of the same substance to produce striking reductions in the blood pressures of animals previously made hypertensive. Inactivated hog renin had had no effect on 1 of these animals when given previously. It is indeed curious that renin from dogs and from other animals prepared in a similar manner had no beneficial effect. The authors make no attempt to explain their results.

It was concluded by Schales, Stead and Warren<sup>128</sup> that the decrease in arterial pressure which they obtained in the treatment of clinical hypertension with renal extracts was nonspecific and had no definite effect on the humoral pressor mechanism. In their opinion the effect of the renal extracts which they prepared was related to the fever, sweating, weakness and severe local reactions produced by the administration of these substances.

Chasis, Goldring and Smith<sup>129</sup> also found that the blood pressure in subjects with hypertension can be reduced by artificial fever induced by intravenous injection of such substances as triple typhoid vaccine and pyrogenic mulin. The reduction in pressure could be maintained in some instances by repeated injection, and the same result could also be achieved when fever was prevented by the administration beforehand of aminopyrine.

They expressed the belief that the mechanism of this reduction is merely a depressing effect on the cardiovascular system and not due to any corrective influence on the mechanism of hypertension.

Friedman, Jarman and Marius<sup>130</sup> came to a similar conclusion in regard to the fall in blood pressure which they observed after subcutaneous implantation of strips of tissue from the kidney, liver and spleen. The depressor effect seemed to be related to the presence of necrotic tissue.

Interest in the possible action of pressor amines, particularly the effect of tyrosinase<sup>131</sup> on them, has continued to arouse interest. Whether this is entirely a nonspecific effect, such as that following the injection of irritant extracts, remains

127 Wakerlin, G. E., Johnson, C. A., Smith, E. L., Gomberg, B., Weir, J. R., Moss, W. G., and Goldberg, M. L. Treatment of Experimental Renal Hypertension with Partially Purified Renin, *Am Heart J* **25** 1 (Jan) 1943.

128 Schales, O., Stead, E. A., and Warren, J. V. Non-Specific Effects of Certain Kidney Extracts in Lowering Blood Pressure, *Am J M Sc* **204** 797 (Dec) 1942.

129 Chasis, H., Goldring, W., and Smith, H. W. Reduction of Blood Pressure Associated with Pyrogenic Reaction in Hypertensive Subjects, *J Clin Investigation* **21** 369 (July) 1942.

130 Friedman, B., Jarman, J., and Marrus, J. Therapeutic Agents and Renal Implantation in Experimental Hypertension, *J Mt Sinai Hosp* **8** 534 (Jan-Feb) 1942.

131 Soloway, S., and Oster, K. A. Inactivation of Pressor Amines by Quinones and Related Diketones, *Proc Soc Exper Biol & Med* **50** 108 (May) 1942. Alles, G. A., Blohm, C. L., and Saunders, P. R. Tyrosinase and Phenolic Pressor Amines, *J Biol Chem* **144** 757 (Aug) 1942. Schroeder, H. A. Effect of Preparation of Amine Oxidase on Experimental Hypertension, *Science* **95** 306 (March 20) 1942. Oster, K. A., and Soloway, S. Studies on the Oxidative Destruction of Pressor Amines, *J Mt Sinai Hosp* **9** 160 (Sept-Oct) 1942.

to be seen. It is curious to note that heat-inactivated tyrosinase as employed by Prinzmetal<sup>132</sup> and his associates had a definite effect in lowering blood pressure, almost equal in fact to that following the use of the enzyme in the active state.

Goldblatt and his associates<sup>133</sup> have reviewed their work on application of a wide variety of therapeutic measures to experimental hypertension in dogs. This is a comprehensive and decisive discussion of the subject, but it is also pessimistic. They emphasize the value of studies of this kind in determining the results to be expected in human hypertension, but it is, of course, obvious that the fundamental differences between experimental hypertension in animals and the most common variety of arterial hypertension in man make comparison of therapeutic effects quite uncertain. The fundamental mechanism is no doubt similar but its application is too different to make the observations comparable for therapeutic use.

It seems safe to conclude that the status of medical treatment of hypertension remains unaltered. The use of the sulfocyanates continues to have its proponents and opponents.<sup>134</sup> The general opinion seems to be that these are the only drugs which have a specific effect in the reduction of blood pressure in the hypertensive state. That this effect can be obtained in experimental hypertension, even though only with an amount which produces toxic reactions, suggests that thiocyanate may have some influence on the humoral mechanism. It is not equally effective, clinically, in all cases. In many instances there is no response, and in some there is reported relief of subjective symptoms without reduction in pressure.

Other drugs, except for the group of sedatives, give little or no lasting benefit, and it has been pointed out again that much of the improvement reported in various medical treatments of this disorder is merely the natural variation of pressure which occurs so characteristically, often only an emotional response and vasomotor activity.<sup>135</sup>

#### A CRITICAL REVIEW OF THE LITERATURE ON VASCULAR SURGERY

Surgical thought this year is naturally focused on war injuries and their treatment. The present review deals with efforts to treat vascular lesions surgically, notable among these are the results obtained from ligation of the patent ductus arteriosus in the presence of subacute bacterial endocarditis.

132 Prinzmetal, M., Alles, G. A., Margoles, C., Kayland, S., and Davis, D. S. Effects on Arterial Hypertension of Heat-Inactivated Tyrosinase Preparations, *Proc Soc Exper Biol & Med* **50** 288 (June) 1942.

133 Goldblatt, H., Kahn, J. R., and Lewis, H. A. Studies on Experimental Hypertension. XVII. Experimental Observations on the Treatment of Hypertension, *J A M A* **119** 1192 (Aug 8) 1942.

134 Caviness, V. S., Umphlet, T. L., and Royster, C. L. Blood Pressure and Sulfocyanates (Thiocyanate), *Am J M Sc* **204** 688 (Nov) 1942. Moia, B., and Quesada, R. Treatment of Arterial Hypertension by Thiocyanate, *Rev argent de cardiol* **9** 41 (March-April) 1942. Tuckwiller, P. A. The Use of the Thiocyanates in Hypertension, *West Virginia M J* **38** 235 (July) 1942. Goldsmith, G. A., and Cordill, S. The Vasodilating Effects of Nicotinic Acid, *Am J M Sc* **205** 204 (Feb) 1943. Cannady, E. W., and Allen, H. N. The Treatment of Hypertension with Potassium Sulfocyanate, *Illinois M J* **82** 146 (Aug) 1942. Quattlebaum, J. T. Treatment of Hypertension. Thiocyanate in Normal Person, *J South Carolina M A* **38** 112 (May) 1942. Russell, W. O., and Stahl, W. C. Fatal Poisoning from Potassium Thiocyanate Treatment of Hypertension, *J A M A* **119** 1177 (Aug 8) 1942. Flaxman, N. Treatment of the Hypertensive Patient in the Precardiac Stage, *Am J M Sc* **205** 696 (May) 1943.

135 Allen, E. V. Why Are so Many Preparations Said to Reduce Blood Pressure in Cases of Hypertension? *Proc Staff Meet, Mayo Clin* **17** 519 (Oct 7) 1942.

## VENOUS OCCLUSIONS

In 30 per cent of 280 autopsies considerable obstruction was found at the mouth of the left common iliac vein. This seems to be a developmental defect, but secondary, postnatal inflammatory reactions may aggravate it. This anatomic study throws an interesting light on the increased frequency of venous occlusions on the left side.<sup>136</sup>

Ligation of the femoral vein, devised as a prophylactic measure against pulmonary embolism when the origin of the thrombus is in the calf, continues to be in favor in properly selected cases. Patterson<sup>137</sup> reported the case of a critically ill sailor with osteomyelitis, thrombophlebitis and pulmonary embolism, after ligation of the femoral vein the patient had no more emboli and recovered. Moore<sup>138</sup> found that of the 39 living patients admitted to the Massachusetts General Hospital after the Cocoanut Grove disaster, 13 per cent presented thromboembolic phenomena, when he considered only the patients with third degree burns requiring a prolonged stay in the hospital, 4 of 9 patients had thrombosis of the veins of the leg. In their cases ligation of the femoral vein was done, below the deep femoral artery, unless the clot had extended past this level. No opaque material was injected in these cases to visualize the clot, since the venograms are often misleading and the procedure is irritating to the intima of the veins.

We have reported on these phlebograms in previous reviews, we thoroughly agree that the help obtained from them is not commensurate with the untoward reactions and the difficulty of interpretation. We do believe however, in the use of anticoagulants after ligation of the femoral vein. According to the physicians specializing in vascular diseases at the Massachusetts General Hospital, neither heparin nor dicoumarin is useful, "since they only prevent further extension of thrombosis and, therefore, do not guard against fatal embolism."

Because the propagating thrombus, which may well occur proximally to the ligature or reside in the pelvic veins, is exactly the part of the thrombus most likely to break loose, the proper use of anticoagulants after operations on large veins has much to recommend it, it also inhibits the propagation of thrombi at the site of the pulmonary embolus, which is often recognizable clinically and at autopsy.

In 3 cases of septic pelvic phlebitis ligations of the ovarian vein and the vena cava were performed. All 3 patients showed a dramatic fall in temperature, all 3 recovered.<sup>139</sup>

## ARTERIAL OCCLUSIONS

Individual reports of successful embolectomies continue to appear. Four cases were reported by Lesser.<sup>140</sup> The number of hours that elapsed between the onset of occlusion and the time of operation were four and a half, twelve, thirteen and fourteen. The attempt at conservative management should not be prolonged beyond six hours after the vascular accident. A riding embolus at the aortic bifurcation was removed at a laparotomy done with spinal anesthesia, the patient died on the

136 Krumbhaar, E. B., and Ehrlich, W. E. A Frequent Obstructive Anomaly of the Mouth of the Left Common Iliac Vein, *T. A. Am. Physicians* **57** 196, 1942.

137 Patterson, J. K. Femoral Vein Ligation for Thrombophlebitis with Pulmonary Embolism, *U. S. Nav. M. Bull.* **41** 512 (March) 1943.

138 Moore, F. D. A Note on the Thrombophlebitis Encountered, *Ann. Surg.* **117** 931 (June) 1943.

139 Collins, C. G., Jones, J. R., and Nelson, E. W. Surgical Treatment of Pelvic Thrombophlebitis, *New Orleans M. & S. J.* **95** 324 (Jan.) 1943.

140 Lesser, A. Embolic Arterial Occlusion of Lower Extremities, *J. A. M. A.* **122** 285 (May 29) 1943.

twenty-seventh postoperative day from a pulmonary infarction<sup>141</sup> In another case death occurred as a result of pulmonary embolism during the extraction of a clot from the common iliac artery, the fatal pulmonary embolus was caused by clots breaking loose from the right auricle of an old rheumatic heart<sup>142</sup>

Murray<sup>143</sup> reported 5 aortic embolectomies done through an abdominal extra-peritoneal approach The circulation was restored in all 5 cases, and the impending gangrene of both legs in each case was immediately replaced by normal circulation in the extremities While 4 of the patients sooner or later died of repeated visceral or cerebral emboli, the results are impressive Certainly the therapeutic problem following embolectomy is the prevention of future emboli The surgeon here must look for guidance to the internist, the pharmacologist and the biochemist The present anticoagulants cannot be given for many months and years, and emboli can occur during administration of heparin, as in 2 of Murray's cases

The response of individual patients to heparin varies a great deal, this observation led to the suggestion that the patient's tolerance to heparin might serve as a test of the clotting mechanism<sup>144</sup> Patients during the first few days after major operations, following thrombosis of any kind and in acute stages of Bueiger's disease exhibited resistance to heparin The test helps to direct the proper dosage, especially when intermittent administration is used

#### WAR INJURIES TO THE VASCULAR TREE AND THE VASOMOTOR SYSTEM

Neurologic, thoracic and orthopedic surgery have been developed to a much higher degree of efficiency in the surgical teaching centers than vascular surgery Ligatures and sutures of lateral wounds of arteries offer more promise during circumstances prevailing in advanced hospitals than spectacular restorative sutures<sup>145</sup> The problems involved in the treatment of traumatized blood vessels were concisely stated by Gage<sup>146</sup> While men who have had unusual opportunity for practicing suture of blood vessels strongly advocate its use instead of ligatures,<sup>147</sup> most medical officers would find it more practicable or would be forced to use a ligature, protecting the limb with a block of the regional sympathetic nerve supply<sup>148</sup> Articles adequately covering this field have been published by Pratt<sup>149</sup> Holman<sup>150</sup> described concussion of an artery leading to segmental spasm, contusion of an artery leading to thrombosis and embolism, and lateral and circular wounds

141 Pearl, F L Peripheral Embolism with Report of Two Cases Successfully Treated by Femoral Embolectomy, in *Medico-Surgical Tributes to Harold Brunn*, Berkeley, Calif University of California Press, 1942, p 371

142 Wikle, H T, and Cabot, N Embolectomy for Riding Embolus of Abdominal Aorta, *Surgery* **13** 264 (Feb) 1943

143 Murray, G Aortic Embolectomy, *Surg, Gynec & Obst* **77** 157 (Aug) 1943

144 de Takáts, G Heparin Tolerance A Test of the Clotting Mechanism, *Surg, Gynec & Obst* **77** 31 (July) 1943

145 McNealy, R W Blood Vessel Surgery in War, editorial, *J Internat Coll Surgeons* **5** 363 (Sept-Oct) 1942

146 Gage, M Traumatic Injuries to Peripheral Vessels in Both Civil and Military Practice, editorial, *Surgery* **11** 983 (June) 1942

147 Goodman, C Blood Vessel Suture Its Use Instead of the Ligature in War Surgery, *Am J Surg* **60** 196 (May) 1943

148 de Takáts, G Vascular Surgery in the War, *War Med* **3**:291 (March) 1943  
Pratt, G H The Treatment of Traumatic and War Wounds of the Vascular System, *Am J Surg* **57** 26 (July) 1942

149 Pratt, G H Surgical Management of Traumatic Lesions of the Arteries, *S Clin North America* **23** 358 (April) 1943

150 Holman, E War Injuries to Arteries and Their Treatment, *Surg, Gynec & Obst* **75** 183 (Aug) 1942

of arteries. Ligation of the artery should always be followed by division. The treatment of arterial and arteriovenous aneurysms is discussed.

Blakemoire and his associates<sup>151</sup> describe a significant set of experiments, in which vitallium tubes were used as a prosthesis to bridge arterial defects. The tube was lined with a segment of vein by a method requiring no sutures. These grafts were successful in contaminated wounds with the help of oral medication with sulfathiazole. The advances in the control of serious infections and the possible use of anticoagulants afford a real basis for success. The authors point out that if the anastomosis can remain patent for fourteen days when the post-traumatic edema subsides, the limb can be saved. Preserved veins for grafts are suggested.

Since the indications for amputation in war wounds are based mostly on the integrity of the main blood vessels, these contributions deserve a thorough clinical trial. While the results of experiments on animals are most encouraging, the single clinical case reported is not yet conclusive. The tubes are not widely available, and the method requires detailed study. Its use will be probably limited to special teams trained for this type of work.

The technical details contained in these articles on traumatic injuries to blood vessels are purposely omitted, since they are not within the scope of this journal.

The incidence of causalgic states, representing painful vasodilatation with edema, osteoporosis and spreading neuralgia, is increasing again. They most often follow partial injuries to nerves or injuries around small joints of the hand and foot. Early recognition and repeated procaine hydrochloride block of the regional sympathetic ganglions are recommended. When the condition progresses to a late stage it may gradually "burn out," leaving much deformity, or become intractable.<sup>152</sup>

The immersion foot syndrome following exposure to cold has been admirably studied by White,<sup>153</sup> who has summarized the previous observations. Survivors of torpedoed vessels have been exposed to cold air and water, prolonged dependency of the legs, malnutrition and vitamin deficiency. The process seems to differ only in degree of chilling and wetting from frostbite, trench foot and shelter foot. This ischemia during prolonged exposure to cold is followed by a period of active hyperemia which is mainly due to the clinical effects of the products of injury to the tissue. Paralysis of vasoconstrictor fibers is an added factor but seems of secondary importance.

In spite of the increased blood flow in the main vessels, the bounding pulse and the increased cutaneous temperature, the cutaneous capillary bed does not seem to receive adequate oxygen for its increased metabolic demand. Capillary permeability increases, and edema, pain and petechial hemorrhages occur. By cooling the skin this disparity between supply and demand for blood is diminished.

The inflammatory reaction and hyperemia subside in a few weeks, and the circulation gradually returns to normal. Neuritic pain, however, makes its appearance when the injured nerves begin to regenerate. In the severe forms, this may

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151 Blakemoire A. H., Lord, J. W., Jr., and Steffen, P. L. The Severed Primary Artery in the War Wounded, *Surgery* **12** 488 (Sept.) 1942, Restoration of Blood Flow in Damaged Arteries. Further Studies on a Nonsuture Method of Blood Vessel Anastomosis, *Ann Surg* **117** 481 (April) 1943.

152 Miller, D. S., and de Takats, G. Post Traumatic Dystrophy of the Extremities, *Surg, Gynec & Obst* **75** 558 (Nov.) 1942. de Takats, G., and Miller, D. S. Post Traumatic Dystrophy of the Extremities. Chronic Vasodilator Mechanism, *Arch Surg* **46** 469 (April) 1943.

153 White, J. C. Vascular and Neurologic Lesions in Survivors of Shipwreck. I. Immersion Foot Syndrome Following Exposure to Cold, *New England J. Med* **228** 213 (Feb. 18) 1943. II. Painful Swollen Feet Secondary to Prolonged Dehydration and Malnutrition, *ibid* **228** 241 (Feb. 25) 1943.

persist for as long as six months. Suitable treatment, as suggested by Commander White, consists of first aid methods against general chilling but never heating the chilled extremity. The affected limb is to be kept cool, elevated and surgically clean. Pressure points on the feet, especially the heels, should be avoided. No rubbing or massage is permissible. For cooling of the limb, simple exposure to room air may suffice. An electric fan placed on a bed table may blow air over the feet, the patient may spray water from an atomizer into the stream of air flowing from the fan.

The naval medical officers at Halifax worked out a method of packing such extremities in ice, which is changed every four hours. The purpose of this pack is to cool the temperature of the skin to a level between 80 and 85 F. These packs have been kept on as long as eleven days.<sup>154</sup>

Buerger's exercises and possible sympathectomy for late stages of the immersion foot are suggested.

The study of another group of survivors reported by Ungley<sup>155</sup> makes it obvious that the vascular and neurologic lesions were greatly aggravated by rapid heating in front of the galley stoves of the trawlers which rescued them and had no medical officers.

It is interesting to note that survivors torpedoed in relatively warm water (around 70 F) also show painful, swollen limbs, but these are predominantly due to dependency, immobility, hypoproteinemia from starvation and multiple vitamin deficiencies. Commander White stressed the point that this syndrome is not identical with the immersion limb and that it calls for a high protein, high vitamin diet.<sup>156</sup>

It is to be expected that further clinical experience and possibly clinical investigations will clarify the optimal prophylaxis, first aid and hospital care of men exposed to freezing cold and chilled wet environment. This seems to be an important subject and has obviously received less study than burns have. Severe freezing of limbs of dogs may cause shock and death and may be prevented by immediate application of pressure dressings.<sup>157</sup> When the human hand is cooled by immersion in cold water (5 C), the swelling may amount to 15 per cent of the original volume in three hours, the protein content of the edema-fluid is around 3 per cent.

The crushing injury to limbs which occurs in persons caught under a wreck and pinned there for several hours has a certain superficial similarity to immersion foot, since severe capillary damage and exudation of protein-rich edema fluid occur. Much experimental and clinical work has been done on this syndrome. It seems that approximately 5 per cent of air raid casualties in an urban area may be of this type. A total of 70 such cases have been reported to the British Medical Research Council. For treatment ample intake of alkaline fluids by mouth, plasma and blood for the shock and cooling of the limb with even elastic compression were recommended by Bywaters.<sup>158</sup> He has shown, with Popjak,<sup>159</sup> that in the rabbit

154 Webster, D. R., Woolhouse, F. M., and Johnston, J. L. Immersion Foot, *J. Bone & Joint Surg.* **24**: 785 (Oct.) 1942.

155 Ungley, C. C., and Blackwood, W. Peripheral Vasoneuropathy After Chilling "Immersion Foot and Immersion Hand," with a Note on the Morbid Anatomy, *Lancet* **2**: 447 (Oct. 17) 1942.

156 White<sup>153</sup>, Webster<sup>154</sup>, Ungley<sup>155</sup>.

157 Fell, E. H., and Hanselman, R. Prevention of Shock and Death by Immediate Application of a Pressure Dressing to the Severely Frozen Limbs of Dogs, *Ann. Surg.* **117**: 686 (May) 1943.

158 Bywaters, E. G. L. Crushing Injury, *Brit. M. J.* **2**: 643 (Nov. 28) 1942.

159 Bywaters, E. G. L., and Popjak, G. Experimental Crushing Injury. Peripheral Circulatory Collapse and Other Effects of Muscle Necrosis in Rabbit, *Surg. Gynec. & Obst.* **75**: 612 (Nov.) 1942.

the human condition of the "crush syndrome" can be simulated with the exception that renal failure and myohemoglobinuria are absent, since rabbit muscle does not contain myohemoglobin. Bywaters and Duncan and Blalock<sup>160</sup> expressed the belief that the local loss of fluid into the crushed limb does not explain the entire clinical picture, the ultimate fatal outcome of long-lasting compressions was due mainly to absorption of toxic products.

The renal lesions occurring in the experimental animal have been studied by Eggleton and her associates<sup>161</sup>. Their observations indicate that the experimental lesions which have been produced by binding the hindlimbs of dogs tightly with rubber tubing and compressing the thigh muscles in a vise for five hours resulted in a picture identical with the clinical syndrome. Severe oliguria with appearance of pigmented urine and a low creatinine clearance occurs. Anuria may follow. The renal damage seems to be in the terminal portion of the proximal convoluted tubules. Their evidence suggests that the main factor in the crush syndrome—after plasma has been restored—is an increased permeability of the renal tubules due to a toxic agent released from the damaged limbs. Certain substances, such as uric acid and phosphoric acid, are known to have a selective action on tubular segments, where the reaction of the urine changes. Such renal changes in men were seen in 2 cases of crush syndrome by Dunn and his associates<sup>162</sup>.

This subject is reviewed here because it revives the toxic theory of shock, which after the last war became relegated to the background in face of the great interest in the local loss of plasma and its deleterious effect on blood volume and general capillary permeability. The toxic component in this syndrome has been acknowledged by such an authority on shock as Blalock<sup>160</sup>. The syndrome is also interesting because it may occur after acute occlusion and release of a main artery. In a case of a central dislocation of the hip with fracture of the pubic ramus, the iliac vessels were obstructed by pressure against the inguinal ligament. Relief of the obstruction by dividing Poupart's ligament was followed by sudden collapse. Death occurred four days later from uremia. The limb became very hard after the release, but circulation remained restored. The kidney showed tubular degeneration and blood in the tubules. The blood urea content rose to 200 mg per hundred cubic centimeters<sup>163</sup>.

Surgeons are well aware that somnolence, "toxic psychosis" and a gradual rise in the nonprotein nitrogen content of the blood not infrequently occur in patients with gangrenous extremities, which may rapidly clear up after amputation.

#### VASCULAR ANOMALIES AND ANEURYSMS

Hemangiomas are inherited as an autosomal dominant from a presumably homozygous man<sup>164</sup>. Their treatment, especially if surgical incision is too deform-

160 Duncan, G. W., and Blalock, A. The Uniform Production of Experimental Shock by Crush Injury. Possible Relationship to Clinical Crush Syndrome, *Ann Surg* **115** 684 (April) 1942, Shock Produced by Crush Injury. Effects of the Administration of Plasma and the Local Application of Cold, *Arch Surg* **45** 183 (Aug.) 1942.

161 Eggleton, M. G., Richardson, K. C., Schild, H. O., and Winton, F. R. Renal Impairment Due to Crushing Limbs in Anesthetized Dogs, *Brit M J* **2** 392 (Oct. 3) 1942.

162 Dunn, J. S., Gillespie, M., and Niven, J. S. F. Renal Lesions in Two Cases of Crush Syndrome, *Lancet* **2** 549 (Nov. 8) 1941.

163 Glen, A. M. Temporary Vascular Occlusion Ending Fatally in Uremia, *Brit M J* **2** 875 (Dec. 20) 1941.

164 Beers, C. V., and Clark, L. A. Tumors and Short-Toe—Dihybrid Pedigree. Family History Showing Inheritance of Hemangioma and Metatarsus Atavicus, *J Hered* **33** 366 (Oct.) 1942.



ing or impossible, is preferably by the use of implanted radon seeds (Johnson <sup>165</sup>, Byars <sup>166</sup>). In a case of cirroid aneurysm of the scalp, Patey <sup>167</sup> used a combination of arterial ligatures (both external carotid arteries) and sclerosing injections into the dilated vascular trunks. The lesion was cured.

Henry gives an excellent historical review of the evolution of surgical treatment of aneurysms <sup>168</sup>. Three cases of traumatic arteriovenous fistula of the common femoral vessels are reported, <sup>169</sup> in which venography located the level of the fistula. The vein distal to the fistula was always normal, in contrast to the segment proximal to it. Ligation of the vein distal to the fistula appeared to have the same beneficial effect on the extremity that ligation of the vein proximal to the fistula has on the heart.

For an aneurysm of the right subclavian artery Wheeler <sup>170</sup> divided a portion of the sternum and retracted it upward with the inner end of the clavicle. He then tied the innominate artery. The patient lived eight years after the operation and then died presumably from a rupture of the aneurysmal sac. An arteriovenous aneurysm involving the left innominate vein and the left common carotid artery was successfully closed by obliterating the sac with three arterial clamps, which the authors were forced to place and leave in situ for twelve to fourteen days. One postoperative hemorrhage occurred a month later, but the patient got completely well and works in a munitions factory, lifting 75 to 100 pound (35 to 45 Kg) weights <sup>171</sup>.

#### THE VASOMOTOR APPARATUS

Learmonth and Richards <sup>172</sup> did an anterior root section from the fifth cervical to the second dorsal segment for athetosis of the right arm. Observations with reflex vasodilatation showed that this extremity responded well, even though the most cranial source of its preganglionic vasoconstrictor fibers was the third thoracic segment.

Vasodilatation after sympathetic block is purely a release from vasoconstriction, but the muscles of the forearm do not participate in the vasodilatation <sup>173</sup>.

Hinsey and his co-workers <sup>174</sup> believe to have shown that after preganglionic sympathectomy in cats a functional reorganization of sympathetic ganglions can

165 Johnson, G. S., and Light, R. A. The Treatment of Congenital Hemangiomata of the Skin, *Ann Surg* **117** 134 (Jan) 1943

166 Byars, L. T. The "Malignant" Hemangioma, *Surg, Gynec & Obst* **77** 193 (Aug) 1943

167 Patey, D. H. A Case of Arteriovenous (Cirroid) Aneurysm of the Scalp, Successfully Treated by Combined Arterial Ligation and Venous Injection, *Brit J Surg* **29** 290 (Jan) 1942

168 Henry, A. K. Some Surgical Aspects of Aneurysm, *Practitioner* **150** 136 (March) 1943

169 Watson, J. R., Lichty, J. M., Hill, J. M., and Miller, R. B. The Use of Venograms for the Localization and Study of Arteriovenous Fistula, *Surg, Gynec & Obst* **76** 659 (June) 1943

170 Wheeler, W. I. de C. Ligation of Innominate Artery for Right Subclavian Aneurysm. End Result, *Brit M J* **2** 422 (Oct 10) 1942

171 Tarnower, H., Lattin, B., and Adie, G. C. Successful Closure of an Arteriovenous Aneurysm Involving the Left Innominate Vein and the Left Common Carotid Artery, *Ann Surg* **116** 700 (Nov) 1942

172 Learmonth, J. R., and Richards, R. L. Note on the Spinal Origin of Vasoconstrictor Fibers to Arm in Man, *Quart J Exper Physiol* **32**:87 (May) 1943

173 Warren, J. V., Walter, C. W., Romano, J., and Stead, E. A., Jr. Blood Flow in the Hand and Forearm After Paravertebral Block of the Sympathetic Ganglia. Evidence Against Sympathetic Vasodilator Nerves in the Extremities of Man, *J Clin Investigation* **21** 685 (Nov) 1942

174 Hinsey, J. C., Geohegan, W. A., and Aird, O. J. Functional Reorganization of Sympathetic Ganglia Following Preganglionectomy, *Tr Am Neurol A* **68** 45, 1942



follow, with reinnervation of postganglionic fibers through the first thoracic segment. If this mechanism operates in man, the preganglionic sympathectomy for the aim might be followed by recurrence through the stellate ganglion.

Epinephrine in small amounts augments the transmission of impulses in sympathetic ganglions but in large amounts depresses it. In clinical shock, a sudden liberation of large quantities of epinephrine may produce a depression.<sup>175</sup>

The importance of removing the ganglion opposite the second lumbar vertebra is emphasized by Atlas.<sup>176</sup> There is no standard arrangement of ganglions, and this way the most important segment is excised.

Shumacker<sup>177</sup> reports a sympathetic denervation of 83 extremities and discusses indication, technic and results, which are in perfect accord with present opinion on this subject. He also reports a good result following lumbar sympathectomy for livedo reticularis. The mottling still remained but became pink. In our experience with a recent case, the dry, warm extremity does not satisfy the patient when the mottling persists, since the cosmetic result is not perfect.

An interesting observation led Shumacker to try lumbar sympathetic block to anesthetize uterine contractions, since the patient with livedo reticularis had a completely painless labor.

Abramson and others<sup>178</sup> investigated the blood flow in poliomyelitic limbs and found that it was not reduced. His argument that such patients should not be subjected to sympathectomy may not hold for all cases, since in a definite group of children the reaction of the paralyzed limb to cold is exaggerated and the swollen plum-colored extremities are benefited by sympathectomy.

#### THE SURGICAL TREATMENT OF HYPERTENSION

The only denervations which produced marked hypersensitivity of the intestinal smooth muscle to epinephrine were found to be those which involved sectioning of the axons passing to the intestines from cell bodies located in the preaortic ganglions.<sup>179</sup> This study confirms the wisdom of cutting splanchnic nerves and lumbar chains for hypertension without injury or excision of the preaortic ganglions. Certainly the clinical disturbances of the gastrointestinal tract after section of the splanchnic nerve are slight compared with those occurring after celiac ganglionectomy, an operation not to be recommended.

A common cause of hydronephrosis in early life is the aberrant renal vessel.<sup>180</sup> It was noted in 0.375 per cent of the autopsies on patients below the age of 12 years. In children simple ligation of such a vessel is better tolerated than in adults, who may need a partial resection of the kidney.

In 5 patients suffering from essential hypertension, renal blood flow was studied before and after sympathectomy. No important changes were noted. The

175 Bulbring, E., and Burn, J. H. Action of Adrenaline on Transmission in Sympathetic Ganglia, Which May Play a Part in Shock, *J. Physiol.* **101** 289 (Nov. 30) 1942.

176 Atlas, L. N. Sympathetic Denervation Limited to the Blood Vessels of the Leg and Foot, *Ann. Surg.* **116** 476 (Sept.) 1942.

177 Shumacker, H. B., Jr. Sympathectomy in the Treatment of Peripheral Vascular Disease, *Surgery* **13** 1 (Jan.) 1943.

178 Abramson, D. I., Flachs, K., Freiberg, J. A., and Mirsky, I. A. Blood Flow in Extremities Affected by Anterior Poliomyelitis, *Arch. Int. Med.* **71** 391 (March) 1943.

179 Youmans, W. B., Karstens, A. I., and Aumann, K. W. Effect of Vagotomy and Sympathectomy on Sensitivity of Intestinal Smooth Muscle to Adrenalin, *Am. J. Physiol.* **137** 87 (Aug.) 1942.

180 White, R. R., and Wyatt, G. M. Surgical Importance of Aberrant Renal Vessel in Infants and Children, *Am. J. Surg.* **58** 48 (Oct.) 1942.

cases presented, however, were such that a flexibility of the renal vascular bed could hardly be expected<sup>181</sup>

Bordley, Galdston and Dandy<sup>182</sup> followed 10 patients from three to seven years after sympathectomy for hypertension—a truly admirable follow-up. Two patients died shortly after operation. Three supradiaphragmatic and 7 infradiaphragmatic operations were done. The sole criterion for operating was the presence of incapacitating symptoms. Relief of symptoms occurred. Postural hypotension was absent in the patients who had supradiaphragmatic operations but present in 4 of the 7 who had infradiaphragmatic ones. In none of the patients was sexual function impaired. The responses to the cold pressor and the sodium amytal test did not change postoperatively. One of the patients who underwent a supradiaphragmatic operation had a good reduction of blood pressure for four and a half years and then had a return to the preoperative level for the two and a half years preceding the report. Postural dyspnea occurred with postural hypotension, this has not been reported before. The best case was that of a 29 year old woman with a hypertension of very short duration.

It is our impression that with a more extended, complete splanchnic section and with a group of patients seen in an earlier stage the results are still better. This is certainly the best postoperative study that has been so far reported.

A group of 54 cases is reported from the Lahey clinic by Bartels, Poppen and Richards<sup>183</sup>. Their indications have gradually changed with increasing experience. The blood pressure must fall to 150 systolic and 100 diastolic while the patient is at rest and under sedation. Of the patients with grade II hypertension 55 per cent obtained a drop in pressure, of those with grade III hypertension 37 per cent were benefited. Of 20 patients more than 40 years old only 2 obtained relief, whereas of 32 patients less than 40 years old 68 per cent had a drop in blood pressure. No persons with grade IV hypertension were subjected to an operation in the more recent series. Four patients had normal kidneys revealed by biopsy, they all obtained clinical relief. It is obvious from this study that surgical treatment of hypertension will have to be urged for persons with much earlier stages, preferably for persons with the asymptomatic forms which are recognized on insurance or preemployment examinations.

#### AMPUTATIONS

Thorek<sup>184</sup> advocates a flapless amputation of the thigh without a tourniquet. He is against the use of spinal anesthesia, because it increases the incidence of thrombosis, he advocates suture of the fascia lata, uses no drainage and injects alcohol into the nerve stump.

Theis<sup>185</sup> reports on 50 amputations for advanced arterial disease, he believes that his mortality is as low as has been recorded in spite of intensive efforts to save the limbs by conservative measures. He has seen aggravation of infection by suction and pressure treatment, by closing the stump in the presence of spread-

181 Findley, T, Clinton E, and Edwards, J C. The Effect of Sympathectomy on Renal Blood Flow in Essential Hypertension, *Surgery* **12** 64 (July) 1942.

182 Bordley, J, Galdston, M, and Dandy, W H. The Treatment of Essential Hypertension by Sympathectomy. A Report on Twelve Patients Three to Seven Years Following Operation, *Bull Johns Hopkins Hosp* **72** 127 (March) 1943.

183 Bartels, E C, Poppen, J L, and Richards, R L. Surgical Treatment of Hypertension. Results in Fifty-Four Cases, *Ann Int Med* **17** 807 (Nov) 1942.

184 Thorek, P. A Simplified Technique for Thigh Amputation, *Surg, Gynec & Obst* **75** 225 (Aug) 1942.

185 Theis, F V. Amputations for Advanced Arterial Disease, *Surg, Gynec & Obst* **76** 35 (Jan) 1943.

ing infection and by local amputation of toes. The author emphasizes the use of the oscillometer but does not use histamine flares for determination of the level of amputation.

McLaughlin<sup>186</sup> recommends pentothal sodium for minor surgical procedures and low spinal anesthesia, with 50 mg of procaine hydrochloride, for major amputations in persons with diabetes. If inhalation anesthesia is necessary, he prefers cyclopropane. In the presence of severe infection, a two stage procedure is employed, the use of drains is advisable in most cases. The two stage procedure and the local use of sulfanilamide will decrease the need for drainage. Follow-up studies revealed that approximately 50 per cent of the patients who had an amputation were dead within one year after discharge from the hospital.

Refrigeration of limbs to prevent absorption of toxins and advance of bacterial infection and to relieve pain prior and during amputation is discussed by McElvenny<sup>187</sup>. Chief pharmacist's mate Kennedy<sup>188</sup> describes a simple ice container for use in amputations.

The reviewed five articles on amputations contain many controversial points. The experiences of the present war may clarify many points. The tendency toward simple procedures, effective safe anesthetic methods and close control of infection is unmistakable. The late sequelae of amputations, phantom limbs and causalgic states, are most stimulatingly discussed in a monograph by Livingston<sup>189</sup>.

#### LIGATION OF THE PATENT DUCTUS ARTERIOSUS

Keys and Shapiro<sup>190</sup> have most enlightening data on 57 adults who had post-mortem evidence of a patent ductus arteriosus. Forty per cent of these died of subacute bacterial endocarditis and 28 per cent of congestive heart failure, 2 patients died of ruptured aneurysm of the pulmonary artery. Inoperable conditions existed in about 17 per cent of the patients. In the adult the ductus is often very short.

The authors have records on 137 operations, nearly half of which have not been published. In 104 of these there was no infection. Thirty-three patients had subacute bacterial endocarditis. Six patients died of hemorrhage during or following operation. The total surgical mortality was less than 10 per cent. A rough calculation would suggest that there are about 20,000 persons in the United States suffering from this anomaly. Attempt at ligation is justifiable in spite of the fact that the patient's circulation seems well adjusted at the time, but it must be expected that difficult or impossible conditions may be encountered.

In a number of articles, Touroff<sup>191</sup> continues his remarkable reports on the closure of the patent ductus in the presence of subacute bacterial endocarditis. He has now done 12 operations, with 7 recoveries, 3 failures and 2 surgical deaths. He points out that in the early stages of infection the vegetations are confined to the

186 McLaughlin, C. W., Jr. The Surgical Management of Diabetic Gangrene, *Surgery* **13** 423 (March) 1943.

187 McElvenny, R. T. The Present Status of Cooling Limbs in Preparation for Surgical Procedures, *Am J Surg* **58** 110 (Oct) 1942.

188 Kennedy, J. A. A Technic and Device for Application of Ice Anesthesia for Amputation of Extremities, *U S Nav M Bull* **41** 226 (Jan) 1943.

189 Livingston, W. K. Pain Mechanisms. A Physiologic Interpretation of Causalgia and Its Related States, New York, The Macmillan Company, 1943.

190 Keys, A., and Shapiro, M. J. Patency of the Ductus Arteriosus in Adults, *Am Heart J* **25** 158 (Feb) 1943.

191 Touroff, A. S. W. Further Experiences in the Surgical Treatment of Subacute Streptococcus Viridans Endocarditis Superimposed on Patent Ductus Arteriosus, *J Thoracic Surg* **12** 1 (Oct) 1942, The Results of Surgical Treatment of Patency of the Ductus Arteriosus Complicated by Subacute Bacterial Endocarditis, *Am Heart J* **25** 187 (Feb) 1943.

ductus and the pulmonary artery, later they may spread to the cardiac valves or to the aorta. Aortic involvement is favored by a short duct. When peripheral emboli have occurred or when other congenital anomalies are present elsewhere, the ligation is not indicated.

The chief dangers of the operations are hemorrhage and injury to the left recurrent laryngeal nerve. In the presence of subacute bacterial endocarditis the likelihood of accidental hemorrhage is increased, because of the friability of the duct. The authors make several technical suggestions, which have resulted in freedom from this complication in the last 4 cases, also the time of operation may be materially reduced.

Other cases are reported by Nixon<sup>192</sup> and O'Connell<sup>193</sup>. It seems that pediatricians and cardiologists should seriously consider the single uninfected patent ductus arteriosus as a surgical indication. Gross has now performed 30 operations, with 2 deaths, Jones, 26, with 2 deaths. These were in cases without infection, obviously the presence of the bacterial endocarditis increases the risk, but, as Touff<sup>194</sup> has demonstrated, even in such cases there is a chance for cure.

In a recent report on 6 patients made by Harrington,<sup>194</sup> 1 had subacute bacterial endocarditis. This 15 year old girl made a dramatic recovery. Harrington has devised a posterior approach through resection of the fourth rib, which seems to have much in its favor.

It is my impression that ligation of the patent ductus arteriosus is one of the most significant advances in vascular surgery.

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192 Nixon, J. W. Ligation of a Patent Ductus Arteriosus. Report of a Successful Case, *Surgery* **12** 31 (July) 1942.

193 O'Connell, W. S. Ligation of a Patent Ductus Arteriosus, *Taft's M. J.* **8** 101 1942.

194 Harrington, S. W. Patent Ductus Arteriosus with Bacterial Endocarditis. Transpleural Ligation Through Posterolateral Approach, Report of Case, *Proc. Staff Meet., Mayo Clin.* **18** 217 (July 14) 1943.

## Book Reviews

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**Behavior and Neurosis** By Jules H. Masserman, M.D. Price, \$3.00 Pp. 269 Chicago The University of Chicago Press, 1943

Dr. Masserman has done a thorough and workman-like job. This is true both of his experimentation and of his study of the various interrelated fields with which his experimentation is concerned. His theoretic approach to the problem—the experimental induction and reduction of “neuroses” in cats—is holistic, and he is at great pains to refute the mechanistic concepts of the representatives of the Pavlovian and the post-Pavlovian school of thought. They, he says, are guilty of entangling themselves in an ever increasing complexity of terminology in an effort to uphold a position which can be more easily and coherently explained by assuming “(a) that behavior is motivated by the needs of the organism, (b) behavior is reactively attuned to the animal’s interpretation of the physical and social meanings of its environment, and (c) that instinctual satisfaction and adaptation may be supplemented even in animals by expressive, substitutive, or symbolic conduct,” (p. 13). This view is held by both the modern and the eclectic school of biologic thought as well as by the psychoanalysts.

He demonstrates that the hypothalamus is not a locus of sensory or affective emotionality but simply a coordinating motor station, stimulation of which produces no meaningful experience for the animal. He observes that frustration alone rarely brings forth neurotic symptoms but that it is necessary to have conflict of two opposing affects.

The therapeutic methods and their relative efficiency are interesting. The most effective method is “working through”, i. e., the animal by being given opportunity to manipulate the conflictful situation plus encouragement from the experimenter gradually overcomes the neurosis and the fear of the situation producing it.

**Synopsis of Diseases of the Skin** By Richard L. Sutton, M.D., and Richard L. Sutton Jr., M.D. Price, \$5.50 Pp. 481 St. Louis C. V. Mosby Company, 1942

The Suttons, *per se*, have collaborated to present in a compact form a general discussion of diseases of the skin. The material is prepared primarily for the physician in general practice rather than for the specialist in dermatology. In order best to use their space, the authors have concentrated on simplicity and condensation, so they devote most of the space to common conditions and allot only a little to unusual ones. To further enhance the essentially practical quality of the book there is an illustration on nearly every page. The illustrations are well selected and for the most part are clearcut and readily interpreted. One minor criticism of the book has to do with the presentation of the systemic diseases which have cutaneous manifestations. One tends to gain the impression that the cutaneous lesions are of primary importance whereas actually the underlying etiologic factor should dominate the whole consideration of the disease. The book can be highly approved and is recommended to practitioners of medicine who see patients with cutaneous disorders only from time to time.

**Kaiser Wakes the Doctors** By Paul de Kruif Price \$2.00 Pp. 158 New York Harcourt, Brace and Company, 1943

Paul de Kruif always writes cleverly and with enviable facility. Here he calls himself a medical reporter, telling in journalistic fashion the story of the medical organization of Mr. Henry J. Kaiser’s ship-building projects.

The book begins with an account of Dr. Sidney Garfield’s twelve bed hospital in Desert Center and shows how the idea back of this—a hospital supported by many small contributions from well persons to insure good care when illness finally comes—was developed later by Mr. Kaiser at Grand Coulee and Permanente, and finally on a still larger scale to include 125,000 workers and then families of the shipyards in Richmond, Oakland and Vancouver, Washington.

Obviously, in Dr. de Kruif’s opinion, Mr. Kaiser has managed to finance the cost of good medical care successfully, and obviously, too, Dr. de Kruif has been much impressed by Mr. Kaiser. He believes that Mr. Kaiser’s methods, adopted to meet a wartime medical emergency, will prove sufficiently durable to carry over into times of peace. Thus he ends with the generality that some form of public health and hospital insurance will come into its own after the war because in all probability the structure of medicine can no longer be supported by charity, by endowments or by large grants of money from a few sources. This will be all right if only a man like Mr. Kaiser continues to spur on the doctors and keep them awake.

The book is written for the general public rather than for the members of the medical profession. It seems to have been put together in a hurry and reads almost as if it had been dictated, so that its literary style is affectedly colloquial. But it is a short volume and easily read.

**Hypertension** By Irvine H. Page, M.D. Price \$1.50 Pp 80, with 7 illustrations Springfield, Ill. Charles C. Thomas, Publisher, 1943

"The person who is suddenly told he has high blood pressure is frightened and bewildered." With this first sentence the reviewer parts company with the author. Doctors should not tell patients about blood pressure in such a way as to frighten and bewilder them; they must go to great pains to accomplish the opposite of this. If they fail, the situation will probably not be remedied by this manual, which may at many points create more alarm from the picture of the arteriosclerotic vessel to the statement that the damaged arteries may give way, and on to the therapeutic advice which is quite sound but of necessity purely general. The truth of the matter is that the whole idea of manuals of this sort, no matter how well they are prepared, is open to question. For diabetic patients a well devised manual is, to be sure, useful if not actually necessary, because of the mathematical data on diet and on sugar in the urine and blood which must be dealt with. When it comes, however, to hypertension, pernicious anemia, gastric ulcer, allergy, etc., such compendiums in no sense can replace the individual advice which the doctor must give to each patient, a fact which most of the writers themselves take pains to emphasize.

**The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects**  
By John R. Paul, M.D., and other contributors, for the American Heart Association  
New York: Metropolitan Life Insurance Company, 1943

The author looks on rheumatic fever as a specific disease, though he admits that there is not uniformity of opinion in so regarding it. The argument centers on the relationship of hemolytic streptococcal infections to rheumatic fever. There is no doubt of the close relationship between the two. Nevertheless it has not been proved that hemolytic streptococci are the only infectious agents in rheumatic fever, and until this question has been settled it is wise to consider it a distinct disease.

Rheumatic fever has been poorly defined and has been neglected in compilations of vital statistics. Only a rough estimate of its incidence and importance can be obtained. However, in the northern half of the country it probably ranks next to tuberculosis and syphilis among the chronic infections.

The period of greatest susceptibility is that of midchildhood, which is due in part perhaps to the fact that there is more opportunity for exposure at this age.

Both environment and inherited tendencies are important in determining the prevalence of rheumatic fever. Among environmental factors, climate, season and living conditions are important. The important features in the living conditions seem to be crowding, poverty and perhaps damp living quarters.

A study of rheumatic families has revealed that there is an inherited tendency to acquire the disease.

The author stresses the fact that the public health aspects of rheumatic fever have been neglected. A first step must be education of physicians, nurses and social service workers to the importance of the problem. Main effort should be concentrated on early recognition of the disease and provision of adequate facilities for the care of those who are already suffering from it.

This excellent monograph deserves the attention of all who are interested in rheumatic fever.

**Allergy, Anaphylaxis and Immunotherapy** By Bret Ratner, M.D. Price \$8.50 Pp 834  
Baltimore: Williams & Wilkins Company, 1943

The title of this book rather belies its contents. One would gather the impression that it was a book on allergy prepared by an allergist for allergists. On the contrary, the author is clinical professor of pediatrics in one of the New York schools and the book has been prepared for the practitioner of medicine who is engaged in the treatment of disease and all its ramifications. Ratner was motivated, as he says in the preface, by a desire to understand allergy. Then having gained knowledge of this very important physical state, it became obvious to him that it would be wise to acquaint the medical profession with the reasons why serums and vaccines were given, why blood substitutes and sulfonamides were an integral part of chemotherapy and why these various agents acted as they did. It would seem that the author has well accomplished his objective. As a practicing physician he presents a clear exposition of the general principles of immunotherapy and the methods of making use of immuno-

therapeutic agents and to these two main sections he has added an excellent description of the allergic state

It is rather interesting that there are some forty diseases or disorders which may be treated by vaccines, serums, toxins and other potent biologic preparations. Most of these diseases are considered to a very wide extent so far as their treatment is concerned. A few of the rarer conditions are not elaborated on in quite so much detail. As the section on treatment (immunotherapy) occupies a goodly portion of the book, it can be seen that the work should be of great value to the practicing physician. For this purpose alone it can be recommended without qualification.

The format of the book is excellent. One criticism might be made of the typography, that is, that some of the illustrations are not particularly clear, due either to poor focusing of the camera which made the pictures or else to the grade of paper that is used in the book.

**Tifus exantemático. Etiología—clínica—profilaxis.** By Prof. Dr. G. Clavero and Dr. F. Perez Gallardo. Pp. 166 and vii, with a prologue by Dr. Jose A. Palanca, Director of Health, Madrid. Graficas Afrodiseo Aguado, S. A., 1941.

This monograph is a concise presentation of classic typhus. After a brief sketch of the history and the geographic distribution, in which are presented data on the recent epidemic in Spain, the disease is described in considerable detail. The etiology, clinical characteristics, pathologic anatomy, immunology, epidemiology and prophylaxis are all well outlined. Laboratory procedures useful in the study of the disease are also included. In an appendix several related rickettsial diseases, namely endemic typhus, tabardillo, Rocky Mountain spotted fever and others, are briefly mentioned for the sake of completeness.

The authors note that vaccination with the vaccine prepared by the method of Cox (United States Public Health Service) was tried in Spain. Their impression is that the vaccine did not protect against infection but that it served definitely to ameliorate an attack of the disease.

In a later publication (*La prueba intradérmica de Giroud en la infección tifoexantemática*, *Rev. San. y Hig. pub.*, December 1942) the same authors report their experience with the detection of immune bodies in human serum by means of a cutaneous test on rabbits. When living rickettsias from egg membranes are injected intradermally, a local lesion, consisting of erythema, nodule formation and sometimes central necrosis, appears within forty-eight hours. If the rickettsias are first incubated with immune serum the lesion does not appear. The test continues to give a positive result for at least eleven months after infection.

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## News and Comment

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**Dr. Nathan S. Davis III of Chicago Honored.**—Dr. Nathan S. Davis III, of Chicago, assistant professor of medicine, Northwestern University Medical School, has been awarded the Distinguished Service Award of the Mississippi Valley Medical Society, consisting of a gold medal and a certificate. The citation in connection with the award reads: "A high type of physician, an able clinician, a very accurate investigator and, last but not least, a writer of syndicated medical advice for the public. While he descends from an illustrious family in medicine, he has carved his own niche in the profession."

## CHRONIC PULMONARY OSTEOARTHROPATHY

### DYSPITUITARISM AS A PROBABLE CAUSE

B M FRIED, M D

NEW YORK

Since Hippocrates reported his observation on the occurrence of fusiform swelling of the terminal phalanges in persons with consumption this phenomenon has been noted repeatedly by physicians, who, though ignorant of its pathogenesis, nevertheless attached great significance to its appearance in wasting patients. The French physician Pigeaux<sup>1</sup> wrote in 1832 "The secret and almost mysterious relationship between phthisis and the state of nails evidently shows that older physicians were inclined to attach importance to small details which even in the 19th century represent elements of good diagnosis."

Interested in small details, physicians of the past overlooked, however, another detail, namely, that fusiform thickening of the phalanges sometimes accompanies a diffuse involvement of the skeleton. When similar widespread lesions were observed, they were not associated with the clubbed fingers and were not looked on as a sequel of a visceral disease, such as a disease of the lungs or heart, but were considered as a malady *in genere*. Indeed, to the latter part of the nineteenth century chronic pulmonary osteoarthropathy was confused with arthritis deformans, acromegaly, Paget's disease of the bones and leontiasis ossea and even with osteomalacia, which was not rare in those years.

Bamberger, in a brief presentation before the *Wiener medizinischer Gesellschaft* in 1889, was the first to record the observation that his patients with clubbed fingers also displayed a thickening of the hands, wrists, feet and legs. Moreover, he found the condition not only in tuberculosis, a belief hitherto entertained, but in bronchiectasis, empyema and congenital heart diseases. Almost simultaneously there appeared an article by Pierre Marie,<sup>2</sup> whose aim was chiefly to clear away misconceptions. "I wish at first," wrote the French clinician, "to clear the field of acromegaly of facts not germane to it." He first reviewed a case of a condition reported by him previously as acromegaly and found it to be a separate entity. By analyzing this case and those with identical symptoms available in the literature he stressed that in all of them the skeletal deformity and the clinical features were not characteristic of acromegaly, also that they were invariably preceded and accompanied by a long-standing disease of the lungs. He then expressed the opinion that the peculiar overgrowth of the bones in these cases, which he labeled *osteo-arthropathie hypertrophante pneumique*, resulted from a primary pulmonary disease. Bamberger,<sup>3</sup> in another and more detailed paper, published in 1891, corroborated Marie's findings.

From the Division of Pulmonary Diseases, Montefiore Hospital  
Aided by a grant from the Rose Lampert Graff Foundation, Los Angeles

1 Pigeaux, J. Arch. gen. de med. **29** 174, 1832

2 Marie, P. Rev. de méd. **10** 1, 1890

3 Bamberger, E. Ztschr. f. klin. Med. **18** 193, 1891



As Paget's disease of the bones was isolated even before Marie's classic description of acromegaly, it ensued that a group of diseases formerly classed with it clinically was dissociated. Moreover, while the pathogenesis of Paget's disease remained obscure, as it still is today, that of acromegaly and of chronic pulmonary osteoarthropathy was thought to have been elucidated. Acromegaly was ascertained to result from an adenoma of the anterior part of the hypophysis, and osteoarthropathy was attributed to circulatory disturbances in the pulmonary circuit or to toxins emanating from the long-standing infection of the lungs.

While the etiologic relationship between the pituitary gland and acromegaly is no longer contested, the causative factor of chronic pulmonary osteoarthropathy remains problematic.

The 4 cases which I had the opportunity of studying in recent years have revealed features which would suggest that contrary to general belief the cause of chronic pulmonary osteoarthropathy may not be remote from that of acromegaly and that here too one is probably dealing with an endocrinopathy caused by a disease that originated primarily in the lungs.

#### REPORT OF CASES

**CASE 1—History**—A carpenter aged 45 years entered the Montefiore Hospital for the first time on Oct. 8, 1932, complaining of pain in the left side of the chest, swelling of the hands and feet and weakness. He neither smoked nor indulged in alcohol. He was married, and his wife and child, 5 years old, were in good health, as were his mother and twelve brothers and sisters. His father died at the age of 73 of carcinoma of the stomach.

The patient became ill in January 1932, experiencing a general malaise accompanied by fever and cough, productive of a small amount of sputum. As treatment at home led to no improvement, he was hospitalized in the middle of April 1932. At this time there were migratory pains in the joints of his hands and feet and pain in the precordium radiating to the shoulder. It was noticed that his left eye was ptotic and that his fingers and toes were noticeably clubbed.

The roentgenograms revealed a dense shadow at the apex of the left lung, which was interpreted as an old tuberculous lesion. The right knee joint showed considerable periarticular thickening and hypertrophy of the synovial membrane with some thickening of the suprapatellar bursa. The left showed in addition an inferior suprapatellar bursitis. The lower under surface and the shafts of the humeri, the radises and the ulnas showed productive periostitis. The laboratory data were noncontributory. He was discharged from the hospital with the diagnosis of fibroid phthisis and chronic pulmonary osteoarthropathy.

His health grew worse, and in July 1932 he was hospitalized in another institution, where his hands and feet were found to be "tremendously swollen." A considerable degree of clubbing and cyanosis of the fingers and toes were also recorded. There was swelling but not pitting edema of the soft tissues of the hands and feet extending above the wrists and ankles. A roentgenogram of the lungs showed a complete "ceiling" of the left apex, the long bones of the hands and feet showed "marked periosteal infiltration." In this hospital, too, the diagnosis was tuberculosis of the apex of the left lung and osteoarthropathy.

The man's health declined, and he lost weight (12 Kg. in one year). On one occasion he had a small hemoptysis. On Oct. 8, 1932 he was admitted to the Montefiore Hospital.

**Examination**—The patient was a tall, well developed man showing evidence of recent loss of weight, he weighed 58 Kg. No dyspnea or orthopnea was noted. His skin was dry but normally warm. His lower jaw was prognathic (fig. 1) and his hands and feet massive. The fingers showed clubbing. The chest was asymmetric, the left hemithorax being flatter than the right. The left supraclavicular and infraclavicular fossae were prominent and tender on palpation. The peripheral blood vessels were not enlarged, and there was no superficial edema. The left lung showed decreased vocal fremitus over the apex, extending down to the second rib anteriorly and to the third rib posteriorly. The percussion note was nearly flat; the voice and breath sounds were diminished, but there were no rales. The skin of the forehead showed considerable furrowing. The abdominal and pelvic viscera and the genitalia showed no abnormalities. There was pain in the left shoulder joint and arm, and motion was limited. The left eye showed Horner's syndrome (fig. 1). The results of the neurologic examination were normal. The diagnosis was carcinoma of the upper lobe of the left lung and chronic pulmonary osteoarthropathy.

A roentgenogram of the chest taken October 11 showed a dense shadow in the apical region extending from the apex down to and just beyond the first rib anteriorly. The shadow was sharply delineated (fig 1). The diagnosis was primary neoplasm of the lung. Roentgen examination of the left shoulder showed periosteal thickening along the shaft of the clavicle, arthritic changes involving the bone forming the shoulder joint and thickening of the periosteum



Fig 1 (case 1)—Tumor of the left superior pulmonary sulcus (bronchiogenic cancer). Roentgenogram of the right hand and the left foot, showing extensive wartlike periosteal overgrowth and tufting of the terminal phalanges. In the inset is the patient's "oval" face, showing prognathism and left Horner's syndrome.

along the shaft of the humerus. A pronounced osteoarthropathy was present in the hands, all the bones appearing considerably broadened and somewhat shorter than normal, with a high degree of periosteal reaction and some sclerosis of bone. The feet, too, showed the same pathologic process (fig 1). There was tufting of the terminal phalanges of the hands and feet. The basal metabolic rate was  $+15$  per cent.

The patient ran a downward course. The Horner syndrome became more accentuated. There occurred a destruction of the first, second and third ribs on the left side and erosion of the left border of the corresponding vertebrae. Paraplegia developed, and the patient died.

**Necropsy**—**Gross Examination** The body measured 168 cm. The lower jaw was prognathic. The hands and feet were voluminous and showed extreme clubbing of fingers and toes, with very slight edema. The edge of the liver extended 4 cm below the right costal margin in the mamillary line. The right lung was free of adhesions, but the left was densely adherent to the chest wall above the hilum. The apical segment of the left lung was replaced by firm tissue which on separation from the anterior portion of the wall of the chest was found to extend up to the base of the neck on the right side, compressing the trachea. There was invasion by tumor of the sternal portion of the first rib and of the posterior portions of the first three ribs. The left side of each of the first three dorsal vertebrae was also eroded.

The heart weighed 470 Gm. The pericardial sac was adherent to the upper portion of the left lung. The myocardium was brownish red and firm. Both ventricles were dilated and hypertrophied, but the valves and the coronary arteries were normal. The pulmonary ring measured 8 cm, the mitral, 10 cm, and the tricuspid, 14 cm. The thickness of the wall of the left ventricle varied from 8 to 13 mm and that of the right from 2 to 4 mm. The pulmonary vessels were widely patent. The aorta showed occasional small atheromatous plaques.

The right lung was normal and the pleural cavity patent. In the left lung, beginning 2 cm below the level of the bifurcation of the main bronchus, the upper lobe was replaced by a fairly well circumscribed tumor. The secondary branches of the upper lobe bronchus were largely obliterated by the neoplasm. The tracheobronchial lymph nodes were firm but contained no tumor. The blood vessels in both lungs were normal. No metastases were present in other parts of this lung or in the right lung, and no abnormalities were noticed in the bronchi throughout the lungs.

The liver weighed 2,000 Gm and measured 20 by 9 by 8 cm. The right adrenal gland weighed 17 Gm, and the left weighed 10 Gm. A minute tumor nodule was visible in each adrenal. The right kidney weighed 280 Gm and measured 14 by 7 by 5 cm. The left kidney weighed 340 Gm and measured 14 by 8 by 6 cm. Both kidneys appeared large and firm but showed no invasion by tumor tissue. The thyroid, too, was considerably enlarged, but there were no visible abnormalities. The testes were small and firm.

The brain and the meninges revealed no gross pathologic changes. The sella turcica was conspicuously enlarged, and the pituitary was twice its normal size.

**Microscopic Examination** Histologic sections showed a stratified squamous epithelial carcinoma of moderate malignancy. Tumor cells were present in the perivascular lymphatics and occasionally in the outer coat of the wall of some vessels. The adrenals contained a few minute clumps of metastatic tumor cells. The striated muscle of the heart showed hypertrophy and fragmentation. The liver showed increase in fibrous tissue in the periportal areas but no proliferation of the bile ducts, the configuration of the lobule was preserved. The spleen showed areas of amyloid. There was atrophy of the testes, with no spermatogenesis. In the pituitary there were hypertrophy and extensive proliferation of the eosinophilic cells.

**Comment**—The principal lesion in this case was a carcinoma of the left pulmonary apex, a so-called superior pulmonary sulcus tumor. Apparently the osteoarthropathy reached considerable dimensions when the neoplasm was still small. In two hospitals where the patient was observed prior to his entry to the Montefiore Hospital the "veiling" of the apex was identified as tuberculous and not carcinomatous. There was no suppuration of the lung or of the tumor at the postmortem investigation.

The appearance of the patient was that of a person with acromegaly, the face was oval and the chin strong, the hands were voluminous and spadelike and the feet were gigantic. This was due to the characteristic periosteal overgrowth as well as to the increase in size of the soft tissues, which were swollen without revealing traces of pitting edema. It is not understood why megalia cutis et ossium should make its appearance in one case and be absent in others.

Not only the extremities (*ακρα*) but the viscera as well were enlarged (*μεγαλα*). The patient showed a splanchnomegaly. As his weight before death was about 52 Kg, the weight of his heart (470 Gm), spleen (430 Gm), kidneys (620 Gm) and adrenals (27 Gm) should be considered as enormously increased.

Tufting of the terminal phalanges characteristic of acromegaly was present in this case too. Finally, the pituitary gland was twice its normal size, revealing a pronounced hyperplasia of the eosinophilic cells. The testes showed atrophy of tubules, with no spermatogenesis.

**CASE 2—History**—A housewife of 61 years entered the Montefiore Hospital complaining of weakness and of constant pain in the lower extremities. Her husband and five children

were living and well. One child had died at the age of 5 years of croup. There had been one miscarriage at the third month of pregnancy, following a fall. Seventeen years prior to her admission, after an episode of irregular vaginal bleeding, her uterus and tubes were

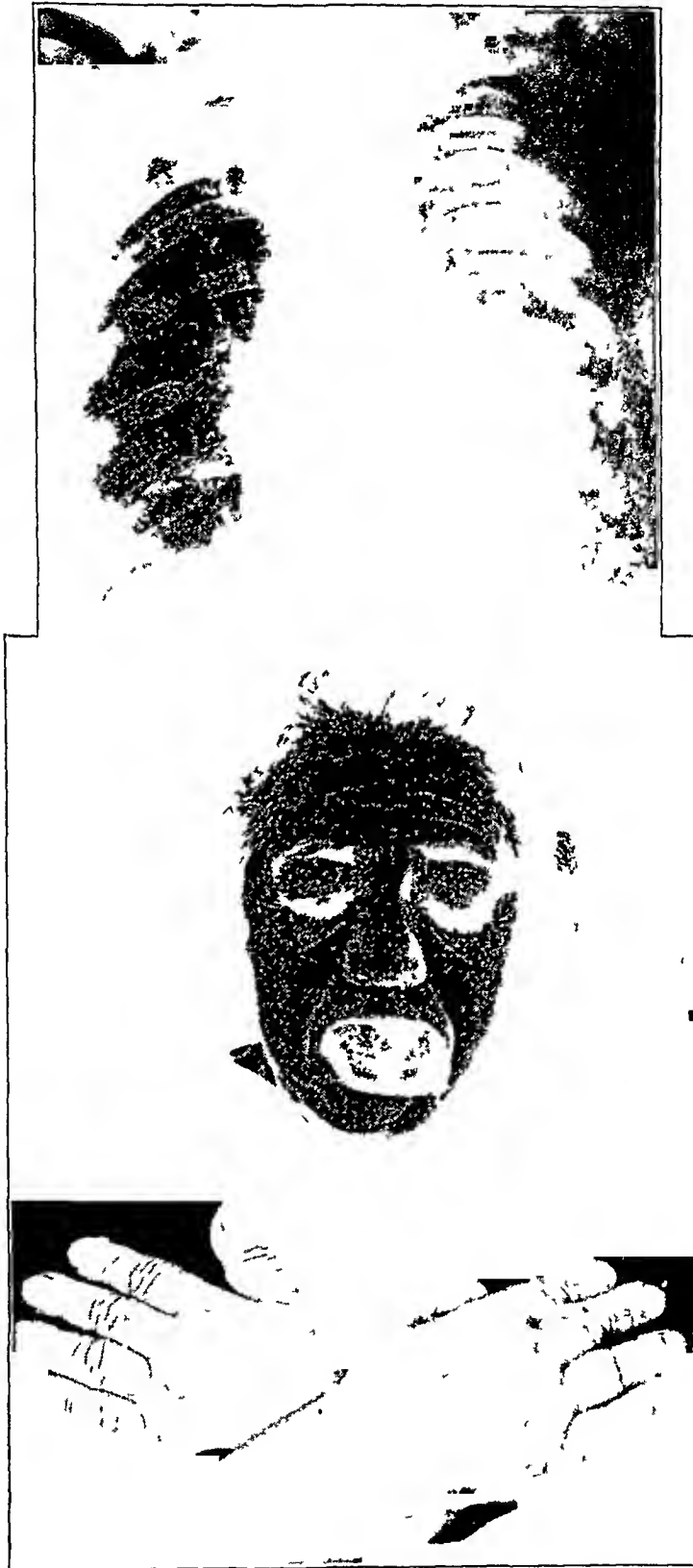


Fig 2 (case 2)—Roentgen appearance of cancer of the lower lobe of the left lung. Photograph of the patient, with redundant eyelids, macroglossia, swollen hands, clubbed fingers and hirsutism.

removed. In 1925 she underwent a perineal operation complicated by an abscess of the right lung which subsided spontaneously. In 1929 her gallbladder was removed, it was inflamed but contained no stones.

Her present illness began in the fall of 1940, with a "cold" which persisted for two months. After that a cough productive of small amounts of sputum developed. Simultaneously her appetite began to deteriorate, and soon pain in the knee joints and legs set in, her fingers commenced to show clubbing.

In February 1941 she entered a hospital, where it was noticed that "her features were heavy and her skin was coarse, dry and thick." Her fingers and toes showed a marked degree of clubbing, the nails were beak shaped. Nothing abnormal was found in the lungs. She was discharged unimproved. A few weeks later she entered the Montefiore Hospital.

*Examination*—The patient was obese despite evidence of recent loss of weight. Her skin was gray and coarse. There was no apparent thinning of the eyebrows, the upper lip showed a considerable degree of hirsutism. Her tongue was noticeably enlarged (macroglossia) and its dorsum was coarsely furrowed (fig 2). There was rounding of the shoulders, and the lips were thick. There were deep corrugations of the scalp resembling the "bulldog" scalp as described by American authors in acromegaly. It could be picked up in large folds, especially around the occipital region. (It could not be photographed because of the growth of hair on the head, which the woman refused to have removed.) Over the forehead, face and upper eyelids, too, the skin was thickened, furrowed and redundant. Forearms, hands, legs and feet were enormously enlarged. The length of the fingers was not affected, but they showed pronounced clubbing (fig 2) and their circumferences as well as those of the hands were greatly increased. The ankles and feet were swollen, with pronounced enlargement of the feet and toes of the same character as in the upper extremities. The circumferences of various structures of the upper and of the lower extremities are shown in the table.

Structure	Circumference, Cm		Structure	Circumference Cm	
	Right	Left		Right	Left
Thumb	6	6	First toe	10.75	10.50
Index finger	9.5	9.5	Second toe	6.75	7
Middle finger	9.75	9.5	Third toe	7	6.75
Ring finger	9.25	9.5	Fourth toe	6.75	6.75
Little finger	9	9	Fifth toe	6.5	6.5

The circumference of the right wrist was 20.5 cm and of the left 19.5 cm, of the right palm 22.25 and of the left 21. The right foot at the ankle measured 28 cm in circumference, the left 29, the right calf measured 31.5 cm and the left 31.5. There was extreme tenderness of the bones of the hands and wrists, also of the lower ends of the radiuses and ulnas. The outer third of the clavicle, too, was extremely tender. The neurologic examination showed no abnormalities, and a bronchoscopic study failed to reveal an endobronchial lesion.

*Laboratory Data*—The basal metabolic rate was +1 per cent. The hemoglobin content was 71 per cent. The white blood corpuscles numbered 7,200 per cubic millimeter, with a normal differential count. The urine was normal. The concentration of sugar in the blood was 123 mg per hundred cubic centimeters of blood, of uric acid, 11.4 mg, of cholesterol, 158 mg, of calcium, 9.4 mg, of phosphorus, 3.3 mg, of albumin, 3.8 mg, and of globulin, 2.4. The phosphatase activity was 5.3 Bodansky units. The blood pressure was 112 systolic and 78 diastolic.

*Röntgenologic Examination*—Chest. A large circular, sharply delineated mass about 3 cm in diameter was seen extending from the left hilum (fig 2). A lateral view revealed the mass to be situated in the midportion of the lung, probably in the upper lobe, close to the hilum.

*Left Shoulder* Including the Upper Two Thirds of the Humerus. There was an irregular periosteal thickening of the bone along the entire shaft of the humerus and along the outer third of the shaft of the clavicle. Hyperostotic changes were noted to involve the acromion process of the scapula, with periosteal thickening along the lateral border.

*Right Shoulder*. There was periosteal thickening of the bone along the outer third of the shaft of the clavicle and periosteal thickening along the medial aspect of the upper third of the shaft of the humerus and the lateral aspect of the lower third.

*Hands*. There were extensive deposits under the periosteum of the phalanges and metacarpal bones (fig 3).

*Left Forearm*. There was irregular periosteal thickening along the shafts of both bones. The thickening was most pronounced along the upper third of the shaft of the ulna and was similar to the changes noted in the hands and feet.

*Legs*. Irregular periosteal thickening was observed along the shafts of both bones.

*Feet*. There were extensive irregular subperiosteal deposits along the shafts of all the metatarsal bones and the proximal row of phalanges (fig 3). There was also periosteal

thickening along the medial and lateral aspects of the shafts of the femurs. The terminal phalanges of the fingers and toes showed tufting (fig 3). The sella turcica was not enlarged, but the cranial bones were thickened.

The clinical diagnosis was acropachyderma with pachyperostosis, tumor of the lung.

Tissue obtained by aspiration from the mass in the chest visualized with roentgen rays showed the growth to be a squamous cell carcinoma. The woman died after seven months in the hospital. Autopsy was not performed.

*Comment*—While in the previous case the pulmonary cancer with Pancoast syndrome fully absorbed my initial interest (the case has been reported from this angle<sup>4</sup>), the appearance of this patient was so striking that the mass visualized in the lungs was relegated to a second rank and the interest was centered on the identification of the extrapulmonary condition. The two diseases were thought to be independent of each other.

Myxedema, to be sure, was the first diagnosis that came to mind. But that she had no hypothyroid disease soon became apparent from her normal basal metabolic rate, her voice, her skin and other signs.

Her general appearance strongly suggested acromegaly of the massive type (*type massif*) as opposed to the giant type (*type geant*) described by Marie. Similar to patients with



Fig 3 (case 2)—Marked thickening of the bones of the cranial vault. Roentgen appearance of hand and foot, with extensive wartlike periostitis and tufting of terminal phalanges of fingers and toes.

acromegaly, she showed involvement of the skeleton, with the characteristic tufting of the terminal phalanges, and soft tissues. Her tongue was enlarged (macroglossia), her features coarse, her eyes puffy, her skull thickened and her scalp redundant ("bulldog" scalp).

The characteristics enumerated brought to mind another condition discussed at some length in Europe but barely touched on in America. The condition was described under various titles: *cutis verticis gyrata*, *pachyacria*, *megalania cutis et ossium*, *pseudoacromegaly* and *acromegalism*. Originally it was believed that the condition represented a variety of diseases until Touraine, Solente and Gole<sup>5</sup> produced evidence to show that in all cases the malady was the same. Gole,<sup>6</sup> an assistant of Touraine, abstracted most of the reported cases in a thesis entitled "Un syndrome osteo-dermopathique, pachydermie plicaturee avec pachyperostose des extremités." Brugsch,<sup>7</sup> in a report of a case thought the name "acropachyderma with pachy-

4 Fried, B. M. *Am J Cancer* 20:791, 1934.

5 Touraine, A., Solente, G., and Gole, L. *Presse med* 43:1820, 1935.

6 Gole, L. *Un syndrome osteo-dermopathique*, Thesis, Paris, Vigot freres, 1935.

7 Brugsch, H. G. *Acropachyderma with Pachyperostitis*, *Arch Int Med* 68:687 (Oct)

periostosis" more suitable. The malady is characterized by new deposits of periosteum around the long bones, by increase in size of the extremities (squaring), by clubbing of the fingers and toes, and by redundancy of the skin of the face and skull. In the cases reported in the literature the disease occurred in young males. It is to be stressed that it was not preceded or accompanied by any other disease of the viscera.

**CASE 3—History**—A childless widow of 55 years entered the hospital in September 1932 complaining of productive cough and pains in the upper and lower extremities. Early in 1930 she was affected by postprandial attacks of vomiting, which were relieved by dieting and gastric lavage. With her respiratory difficulties unabated she was admitted to a hospital, where a roentgen examination revealed a shadow occupying the mesial portion of the lower half of the upper lobe of the right lung. With the bronchoscope an infiltration of the right main bronchus extending into the upper lobe bronchus was seen. She was subjected to treatment with roentgen rays, but this was soon abandoned because of repeated hemoptyses and constant blood streaking. She was discharged from the institution unimproved.

The mild pain in the extremities which had existed for some time became aggravated, and motion became painful. She lost weight and strength. She was then hospitalized at the Montefiore Hospital.

**Examination**—She appeared frail and undernourished. Her chin and upper lip were covered with a thick growth of hair. The hirsutism had appeared about one year previously, at which time her skin began to take on a brownish hue, she was never bronzed. There was considerable puffiness around her eyes, giving her a mongoloid appearance. There was a general adenopathy, and the cervical veins showed dilatation. Her extremities were massive in contrast to her frail body, which weighed 40 Kg. The extremities throughout their entire length were thick, round and shapeless, which gave her a grotesque appearance. The hands were wide and spadelike. The distal phalanges were clubbed, and the distal portions of the radii and ulnae were greatly widened. There was no pitting edema.

The right hemithorax was retracted, and the trachea was deviated to this side. There was dullness to percussion, and rales were heard throughout the entire right lung, the left lung showed no abnormalities. The liver was palpable several centimeters below the costal margin, but there was no tenderness on palpation of the abdomen. The blood pressure was 160 systolic and 100 diastolic. There was a mild hypochromic anemia. The basal metabolic rate oscillated between +18 and +25 per cent. There was severe trismus, the separation between the upper and the lower jaw being no more than a few millimeters, the separation could be made only by force.

**Roentgen Examination**—Chest. A fairly large mass, the size of a lemon, extending out from the right hilus and spreading toward the parenchyma was noticed. The middle and lower lobes contained a few metastatic nodules, and the pleura seemed to be thickened (fig. 4).

**Bones**. The bones were moderately atrophic, showing extensive periosteal thickening along the entire extent of the shafts of the humeri (fig. 4). The hands revealed periosteal thickening along the metacarpal bones, the phalanges, the radii and ulnae (fig. 4). There was tufting of the terminal phalanges of fingers and toes.

**Course**—The patient declined slowly and died after several months in the hospital.

**Necropsy**—Gross Examination. The body was that of a poorly developed and considerably emaciated woman, 145 cm in length. The skin was pale and sallow, the hair was gray, coarse and abundant. The upper eyelids were puffy, producing a mongoloid appearance. The chin and upper lip were abundantly covered with hair. All extremities showed a high degree of osteoarthritis. The distal phalanges revealed a pronounced clubbing and the distal portions of the arms a noticeable widening.

The left lung was free from adhesions and appeared normal, while the right was firmly adherent to the chest wall. It was about one half the size of the left, its pleura measuring 5 mm in thickness. The upper lobe was fibrous and atelectatic. At the hilus all lobes showed infiltration by a tumor mass measuring 3.5 cm in diameter. The growth began about 1 cm below the bifurcation and grew downward along the peribronchial tissue, virtually enveloping the bronchi. The right main artery was surrounded by the greatly thickened pleura, which was infiltrated by tumor so that its lumen was narrowed. The superior vena cava, too, was encircled by the thick pleura, which distorted its course and narrowed its lumen. The tracheobronchial lymph nodes were invaded by tumor. The heart, liver, kidneys and spleen were normal in appearance. The left adrenal gland showed a cortical adenoma measuring 0.5 cm in diameter. The thyroid showed several adenomas. The uterus contained myomas, and the ovaries were small and fibrous. The brain, the pituitary body and the pineal gland were seemingly normal. The anatomic diagnoses were bronchiogenic carcinoma on the

right side with metastases to the left lung, the left kidney, the spleen and the vertebral column, hirsutism, cortical adenoma of the left adrenal, adenoma of the thyroid, myoma of the uterus, diffuse pulmonary osteoarthropathy

**Microscopic Examination** Histologically the tumor was a stratified squamous epithelial carcinoma. The diseased lung showed wide areas of fibrosis due apparently to radiation

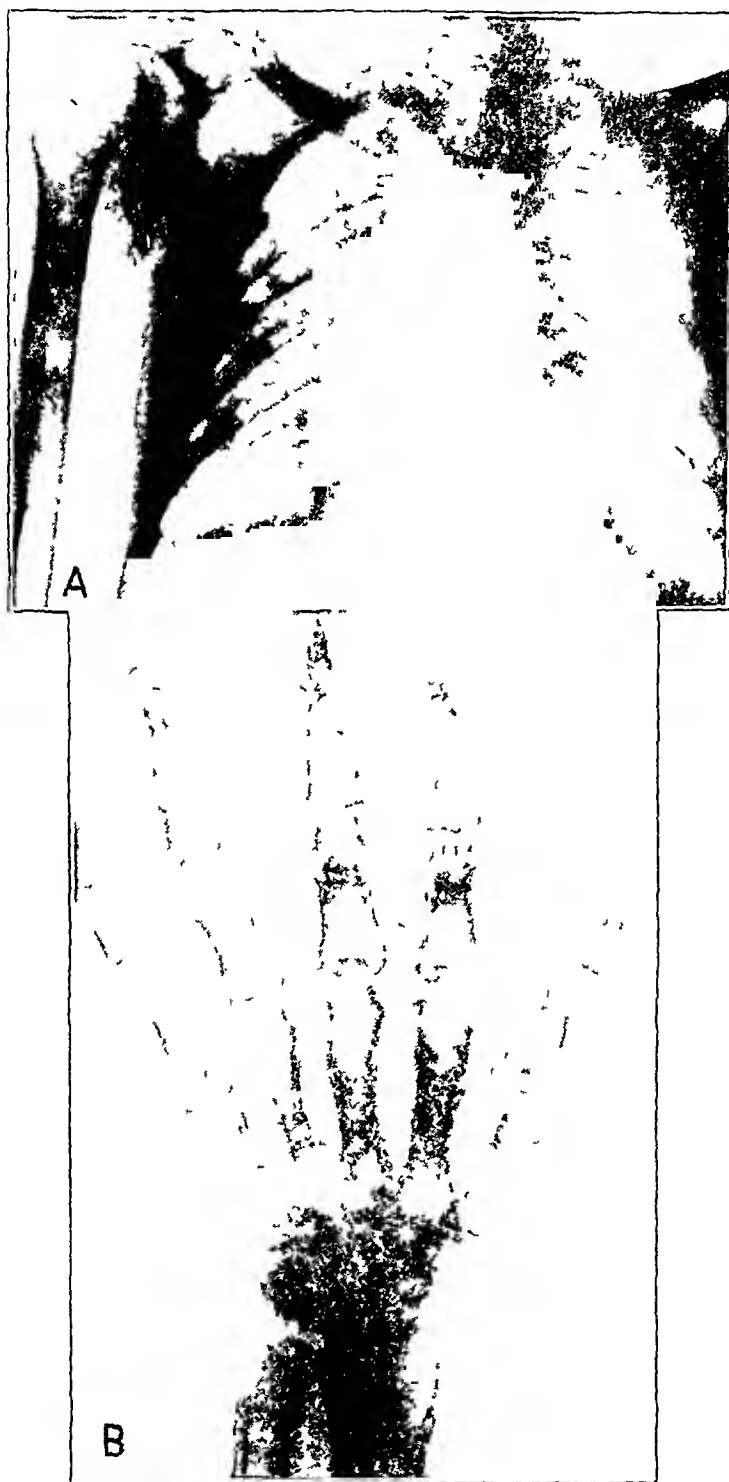


Fig 4 (case 3) —*A*, cancer of the lower lobe of the right lung. The right humerus shows periosteal overgrowth. *B*, roentgen appearance of the left hand, with periostitis of the phalanges, ulna and radius and some atrophy of bones and tufting of the terminal phalanges

therapy. The thyroid showed a moderate degree of colloid goiter and several adenomas. The adrenals, too, showed a sizable adenoma. In the pituitary there was hyperplasia of the cells of the anterior lobe with eosinophilic elements in the majority



*Comment*—In this case the tumor took origin in the mucosa of the right main bronchus, forming a relatively small mass at the hilus of the lung. The fibrosis and shrinkage of the pulmonary tissue were due to the radiation therapy rather than to the neoplasm, culminating in the mutilation of the bronchi and blood vessels.

As in other cases of this group the megalia cutis et ossium became manifest clinically prior to that of the malignant new growth. As in the other cases, too, this aspect of the disease was merely recorded and otherwise was neglected.

The consensus was that the woman had myxedema in addition to her pulmonary cancer. It is of interest that whereas carcinoma rarely develops in a patient with hyperthyroidism its occurrence in a patient with hypothyroidism (myxedema) is not uncommon. At necropsy one adrenal and the thyroid showed sizable adenomas and the pituitary showed hyperplasia of the oxyphilic cells.

*CASE 4—History*—A manual laborer 41 years of age, whose wife and 17 year old daughter were in good health, was admitted to the Montefiore Hospital in March 1937. His father, a sufferer from asthma for many years, had died at 65 years of a cause unknown to the patient. His mother had died at the age of 32 years after a miscarriage. Ten stepbrothers and sisters were in good health.

The onset of illness dated back to the latter part of 1935. It started with painful swelling involving successively the ankles, knees, upper extremities and shoulder joints. From April to October 1936, he was under observation successively in three hospitals. The report of the diagnosis in the first hospital (October 1936) read as follows:

The lungs and the heart showed no abnormalities. The upper extremities showed limitation of and pain in all joints on motion. The wrists and elbows were swollen and warm. The hands were considerably enlarged and swollen, as were the proximal interphalangeal joints. The knees, ankles and feet, too, were hot and tender on motion, motion was limited. The feet were considerably enlarged. There was marked swelling of the breast. Bronchoscopic examination failed to reveal abnormalities, but an aspiration biopsy of the lung revealed tumor tissue which suggested metastatic carcinoma. The Wassermann and Kahn reactions were negative, and the exudate from the joints showed no abnormalities. The patient was discharged from the hospital after two and one half months. Two weeks later he was readmitted to the same institution. In the interval he had gained 2 Kg. in weight, but a productive cough, small hemoptyses and dull pain in the right hemithorax had developed. Pain in the knee joints became aggravated and their motion more restricted. His temperature averaged 101.5 F. His features were coarse, his breasts were considerably enlarged and the extremities were massive. The pain in the joints was so severe that large doses of sedatives were required to afford minimal relief. In the right lung there was an area of dullness, bronchovesicular breathing, decreased vocal fremitus and moist rales were found anteriorly between the fourth and the sixth ribs. On roentgen examination the shadow in the right lung visualized previously was now larger. There was loss of normal tapering of forearms. The erythrocyte sedimentation rate was 55 per cent. He was discharged and shortly after entered the Montefiore Hospital.

*Gross Examination*—At Montefiore Hospital the following observations on admission were recorded. There was evidence of considerable loss of weight. The joints of the hands, shoulders, feet and knees were severely swollen and painful. The lower limbs were massive, clumsy and shapeless. The tibiae showed anterior bowing (fig 5). The hands were particularly striking, resembling spades or paddles with the fingers showing pronounced clubbing (figs 5 and 6). The joints of the knees and ankles contained small amounts of fluid. There was general adenopathy and gynecomastia. The lower two thirds of the right lung were dull to percussion, and the breath sounds in this area were barely audible. His features were coarse and the color of the skin somewhat bronzed, though not pigmented.

*Roentgen Examination of Bones*—There was an enormous periosteal reaction with bone production about the shafts of the femurs, tibiae, fibulae and metacarpal bones. There was extreme thickening and irregularity of the periosteum along the shafts of the humeri, ulnae, radiuses, tibiae and fibulae (fig 5). In the pelvis there were hypertrophic changes along both ilia and femurs. The sella turcica was large, but there were no evidences of destruction.

*Bronchoscopic Examination*—Bronchoscopic examination revealed a large friable mass completely occluding the bronchus of the lower lobe of the right lung below the apical branch.

*Diagnosis*—The clinical diagnoses were bronchiogenic carcinoma of the right lung, chronic pulmonary osteoarthropathy, endocrinopathy.

*Course*—The patient died after five months in the hospital.

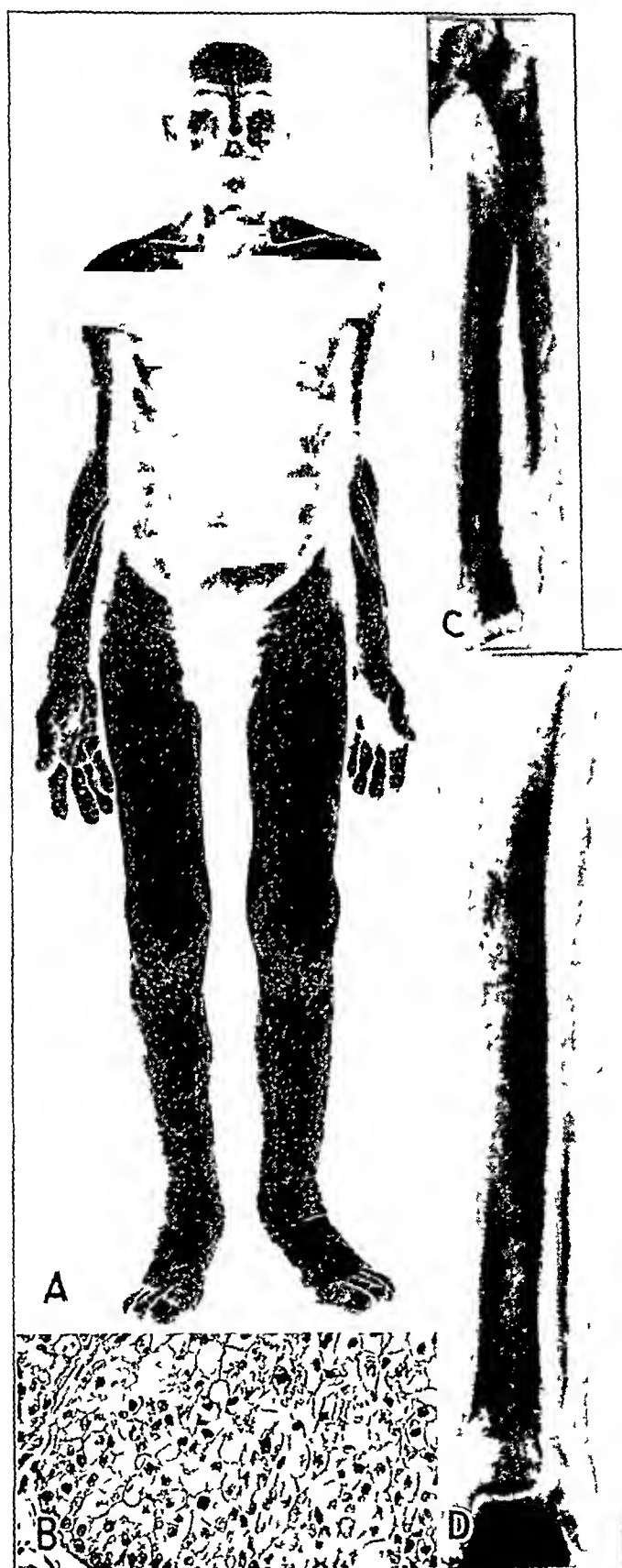


Fig 5 (case 4)—*A*, photograph of the patient, *B*, histologic structure of the bronchial cancer, *C*, roentgen appearance of the ulna and radius, *D*, tibia and fibula with extensive periosteal overgrowth

*Necropsy*—The body was that of a well developed and moderately emaciated man. The features were coarse, and the mandibulum was prognathic. The hands were spadelike, with sausage-like, clubbed fingers. The left tibia was slightly curved anteriorly and was thicker than the right. Both were extremely swollen and shapeless, showing, however, an insignificant degree of edema. The feet were large and flat, and the toes were clubbed. The pleural cavities showed no fluid. The pleura of the left lung was smooth, and the lung showed no gross changes. The right lung was adherent to the wall of the chest and the diaphragm. The lower lobe of the lung was voluminous and firm. A tumor measuring 8 cm. in diameter and extending from the hilus was found in the midportion of the lobe. Apparently it arose in

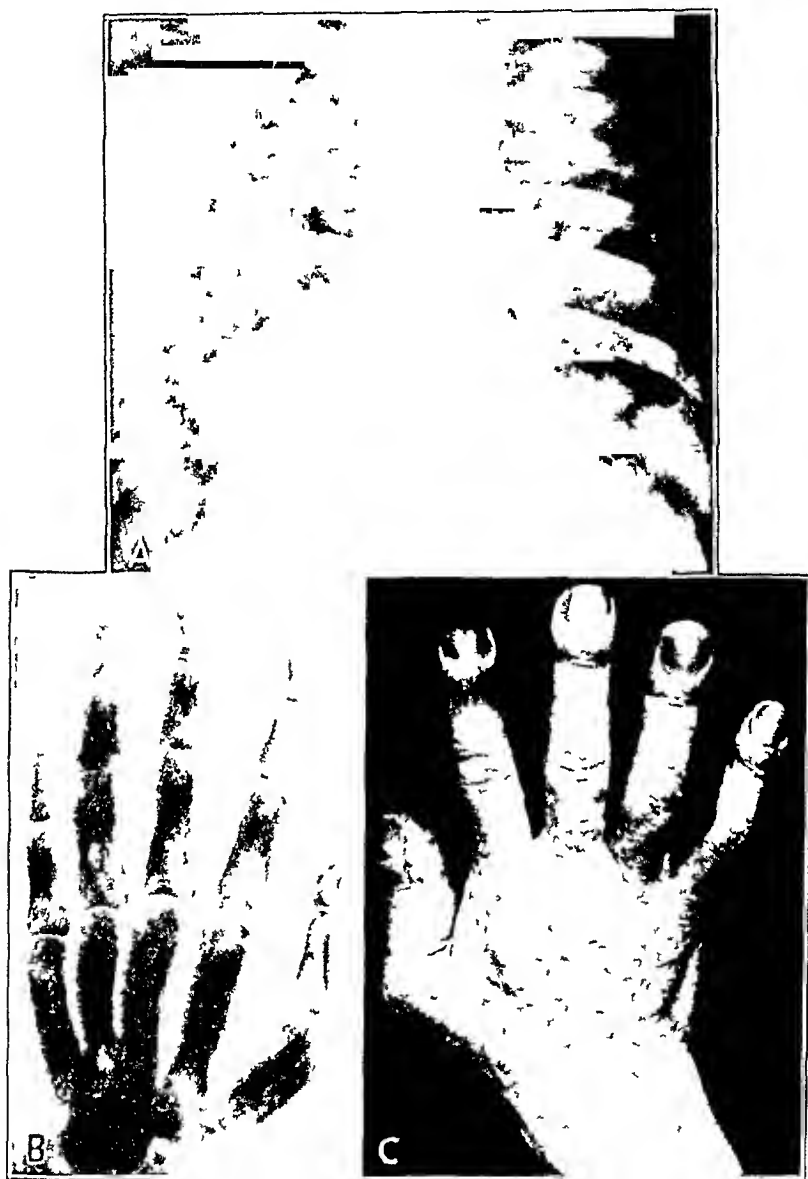


Fig 6 (case 4) —*A*, carcinoma of the lower lobe of the right lung. *B*, roentgen appearance of the left hand, showing lamellary periostitis. *C*, photograph of the right hand, with clubbed fingers.

the mucosa of a small bronchus and spread in a fanlike shape toward the periphery. It was soft, lobulated, hemorrhagic and partly necrotic. The large vessels and bronchi were patent. The heart was of moderate size and the aorta of normal elasticity, with a few plaques of atherosclerosis. The coronary arteries were patent. The liver was normal, but the spleen was slightly enlarged and firmer than usual. Other abdominal viscera showed no deviation from normal, except for the adrenals, which showed several cortical adenomas. The thyroid showed no abnormalities, but the anterior lobe of the pituitary was rather prominent. The genitalia were normal on gross examination.

Microscopically the tumor was made up of large polygonal cells with a sharply delimited clear cytoplasm and an eccentric nucleus rich in chromatin. The cells were gathered in large nests separated by fine fibrous partitions containing small clefts filled with red cells (fig 5). Mitotic figures were common. Necroses and hemorrhages were common throughout the new growth. Areas of typical squamous carcinoma alternated with another type, described by some European pathologists as paramalpighian. In the metastases the new growth was diffusely of the paramalpighian variety. Other viscera, except for the spleen, which showed amyloid, were within normal limits. The pituitary showed hypertrophy and hyperplasia of the eosinophilic cells of the anterior lobe.

*Comment*—Continental physicians disputed Marie's contention that the bones as well as the joints are involved in the process. They were opposed to the term *osteoarthropathy*. Although pathologic changes were not found in the joints of this patient, clinically they all showed swelling, exudate and exquisite soreness.

The osteoarthropathy in this case, as in other cases of this series, manifested itself clinically before the pulmonary disease became evident. Its progress was rapid and stormy. It was attributed to an endocrine disturbance the nature of which was not understood.

The pulmonary circulation showed no deviation from the normal. The adrenals showed several adenomas, the thyroid was above the average weight, the pituitary, too, was enlarged and under the microscope showed hyperplasia of the oxyphilic cells.

#### COMMENT

The pathogenesis of diffuse osteoarthropathy occurring in chronic pulmonary diseases is as obscure today as it was when Marie first described it. The conception of Pigeaux,<sup>1</sup> postulated in 1832 for clubbed fingers, is thought to hold equally true for the disease as seen in the patients herein presented. Pigeaux stated "Three years of investigation have shown that the formation of curved nails is influenced by embarrassment in respiration and circulation, generally it occurs in all conditions affecting 'hematosis'." Marie in his original paper attributed the symptom complex to the selective absorption of toxins from the affected lung. Crump,<sup>8</sup> from Erdheim's laboratory, stated "There is an abnormal substance circulating in the blood which affects the periost, the bones, the joints and the soft parts of the terminal phalanges, as evidenced by clubbing of the fingers." It may be seen that the soft parts are affected not only in the phalanges but in the limbs throughout their entire length.

Before presenting the discussion on the problem of the nature of this phenomenon it is desirable to review briefly its pathologic anatomy.

Observations indicate that not all bones are affected with equal intensity. The tibia and humerus are more intensely involved than other bones, and in the same bone the lesion is more severely developed in the diaphysis than in the epiphysis. As in all diseases of the skeletal system, the process involves both the bone and the periosteum. In the former, new bone formation (hyperostosis) is seen here and there. The picture, however, is dominated by osteoporosis, there is thinning out of the corticalis and the compacta. In the periost it manifests itself as a periostitis (osteophytosis).

The periost is normally composed of dense fibrous tissue. Whenever formation of new bone is called for and whenever there is destruction of bone a new layer, the cambium, is formed on the inner surface of the preexisting periost. The cambium differs from the old periosteal layer in its poorer content of reticulum fibers, of cellular elements and of blood vessels. The cambium, and not the original periost, serves as matrix for newly formed bone. The intimate mechanism of the transformation of the cambium into bone is not understood. It may be ushered

8 Crump, C. Virchows Arch f path Anat 271:467, 1929

in by local or by general conditions, by action of microbes (syphilis, osteomyelitis) or by a general disturbance, as in the cases herein presented. It may be localized, or it may be diffuse.

By studying different parts of the bone one finds different stages of the process, which has enabled investigators to reconstruct the life history of the disease. Thus it was established that the new periost is formed layer by layer, the new layer being superimposed on the one already existing, which gives to the newly formed structure a lamellary appearance visualized with the roentgen rays. Usually the new periost envelops the bone as the bark envelops a tree, its surface having a porous or wartlike appearance (figs 1, 3, 4, 5 and 6). It is significant that osteoporosis is also present in bones and in areas of bones where no new periosteum was formed. It is, then, even possible that the disease originates primarily not in the periosteum, as is almost universally believed, but in the bones. However that may be, the process is that of a hyperplastic porotic osteoperiostitis. As a result, the bones are considerably thickened and disfigured, they are not elongated.

Not only the bones but the soft tissues as well are involved. There occurs a considerable thickening of the skin and subcutaneous tissue of the hands and feet, which produces the characteristic appearance of the extremities in chronic pulmonary osteoarthropathy. There is, then, a *megalia cutis et ossium*. The skin is soft and doughy but shows no pitting edema.

Hitherto pathologic changes of the nature described were said to be present uniquely in osteoarthropathies, occurring in tumors (primary or metastatic) and in certain chronic purulent conditions of the lungs.

In the comment to case 2 attention was drawn to a new entity isolated by French clinicians (Touraine and Golé) under the name of *pachydermie plicaturée avec pachypériostose des extrémités*. Patients affected with this malady show characteristic clubbing of the fingers and toes, squaring of the extremities, thickening of the skin and deformities of the long bones with lamellary deposits of periost. Differing in some details from pulmonary osteoarthropathy, the condition is, on the whole, an exact counterpart of that in the cases herein presented. The pathologic and roentgenologic similarities of the skeletal and cutaneous systems in the two diseases are identical to the finest details. In a case recently reported by Brugsch<sup>7</sup> the similarities were striking. It is particularly significant that the malady does not develop on the basis of a cardiorespiratory or other visceral disease. The consensus is that the disease in these patients is of endocrine origin.

Prior to the isolation of this symptom complex by Touraine and co-workers cases of this condition were reported under the designation of pseudoacromegaly or acromegalism, because of their close resemblance to acromegaly, the endocrine origin of which is today firmly established.

It is well to stress that in acromegaly, as in pulmonary osteoarthropathy, the bones are not elongated, their increase in size being due to the increase of both the periosteal and the subcutaneous tissues. Microscopically, too, the structural changes in the two diseases are closely related. The tufting of the terminal phalanges of fingers and toes, regarded by Cushing and others as an osteologic sign pathognomonic of acromegaly, is likewise present in the disease described by Touraine as well as in pulmonary osteoarthropathy. Tufting of the terminal phalanges of fingers and toes was pronounced in all 4 of my patients. Generally the process in the three diseases affects the same system, the mesoderm. The pathologic changes may vary in degree, and their advance may differ in tempo, but qualitatively they are essentially of the same nature.

The difficulties in the differential diagnosis between pulmonary osteoarthropathy, pachydermia with pachyperiostosis and acromegaly is demonstrated in the case of the Hagnei brothers. In 1868 their disease was defined by Friedrich<sup>9</sup> as hyperostosis of the entire skeleton. In 1888 Erb identified their disease as acromegaly. Marie, too, at first interpreted the condition as acromegaly but subsequently changed his interpretation to pulmonary osteoarthropathy. In 1899 Steinberg<sup>10</sup> stated that the disease of the Hagners was distinct both from acromegaly and from osteoarthropathy. At present it is included in the group of pachydermia with pachyperiostosis.

The foregoing facts and the data obtained from the study of the cases here reported favor the conception that diffuse osteoarthropathy found in neoplastic diseases of the lungs is in all probability caused not by toxins (*masmata imaginaria*, to use Osler's expression) or by circulatory disturbances, as postulated more than a century ago, but by an endocrine imbalance akin to acromegaly and to pachydermia with pachyperiostosis.

Regrettably, cases of chronic pulmonary osteoarthropathy hitherto reported in the literature (numbering about 100) have never been studied from this angle. Attention was generally drawn to the bones and the lungs, while metabolic and endocrine possibilities were totally ignored. Clinicians never went beyond Pigeaux's and Marie's hypotheses. Apropos of a case of this kind which I observed in 1928 I wrote<sup>11</sup> "His appearance was most impressive, resembling somewhat, that of an acromegalic. His features were rather large and disproportionate and the joints looked as if there was a subluxation. The lower jaw was prominent."

An analysis of the 4 cases here reported (deficient though their study may be from an endocrinologic point of view) revealed data pointing toward the conception that the megalia cutis et ossium resulted in all probability from a disturbance in the function of the organs of internal secretion. Summarily the data are: in case 1 acromegalic appearance of the patient, tufting of the terminal phalanges of the fingers and toes, splanchnomegaly, atrophy of the testicles and a large adenohypophysis showing pronounced hyperplasia of eosinophilic elements, in case 2 acromegalic appearance of the patient, "bulldog" scalp, hirsutism, macroglossia, tufting of the terminal phalanges of the fingers and toes and thickening of cranial vault, in case 3 mongoloid features of the patient, secondary male characteristics, large cortical adenoma of the adrenals, several adenomas of the thyroid and hyperplasia of cells of the anterior lobe of the pituitary, with eosinophilic cells in the majority, in case 4 coarse acromegalic features, gynecomastia, several cortical adenomas of the adrenals, roentgenologic evidence of enlargement of the sella turcica and tufting of the terminal phalanges of the fingers and toes.

That the lungs are endowed with functions in addition to respiration has been stressed on many occasions. Various writers have attributed to the lungs a role in the metabolism of lipids. This was suggested by the fact that absorbed albumins and carbohydrates pass directly into the liver while fatty substances are transported by way of the lymphatics and the thoracic duct to the right side of the heart and to the lungs. Fort,<sup>12</sup> in 1867, suggested that the lungs are

9 Friedrich, N. Virchows Arch f path Anat 43 63, 1868

10 Steinberg, M. Acromegaly, London, New Sydenham Society, 1899

11 Fried, B. M. Primary Carcinoma of the Lungs, Baltimore, Williams & Wilkins Company, 1932, p. 117

12 Fort, A. J. A. Anatomie et physiologie du poumon considere comme organ de secretion, Paris, A. Delahaye, 1867

characteristically secretory organs, and he used the term *la glande pulmonaire*—the pulmonary gland. In recent years Roger<sup>13</sup> and his associates, Aschoff<sup>14</sup> and others<sup>15</sup> have subscribed to this conception.

Apparently the functions of the lungs are multiple, and their interrelation with other organs, particularly of internal secretion, is complex and worthy of further study.

As to the interdependence of tumors of the lungs and the organs of internal secretion no information is available, to my knowledge.

#### SUMMARY

Four cases of chronic pulmonary osteoarthropathy in patients with bronchiogenic cancer are reported. Evidence is produced to show that the condition is in all likelihood caused by an endocrine imbalance (dyspituitarism).

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13 Roger, G. H., and Binet, L. *Rev. de med.* **42** 1, 1925.

14 Aschoff, L. *Ztschr. f. d. ges. exper. Med.* **50** 52, 1926.

15 Fried, B. M. Defensive and Metabolic Apparatus of Lungs, *Arch. Path.* **6** 1008 (Dec.) 1928, Lungs and Macrophage System, *ibid.* **17** 76 (Jan.) 1934.

# PREPARATION OF SYNTHETIC IMMUNE SERUM AND NATURE OF IMMUNITY

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Prior to the work of Woehler, who synthesized urea more than a century ago, vital processes and products were considered inseparable from the living body, and the doctrine of vitalism proclaimed them forever beyond the poor power of mankind to understand or reproduce. The tiny crack produced by Woehler in the structure was enlarged by many others, and vitalism is long since defunct. Among the ruins, however, there remains hidden certain knowledge which still awaits excavation. It is with such a fragment, namely the enigma of immunity, that this report is concerned.

## THEORY

It has long been recognized that antibodies are carried in close association with the globulin fraction of the blood plasma. While certain workers, notably Huntoon<sup>1</sup> and Olitzki and Frankel,<sup>2</sup> attempted to separate them from all protein substances, others considered that this is impossible and accepted the belief that they are themselves globulins of a specialized form. In the past decade this viewpoint has been adopted by a great majority of investigators. Felton<sup>3</sup> was among the first to voice this conviction, and many others have followed his lead.

In the past proteins have been separated by precipitation with increasing concentrations of a salt and classified on this basis. The antitoxic serums, such as that used in diphtheria, have been found associated with the pseudoglobulin, a fraction which is carried down by a 50 per cent saturated solution of ammonium sulfate and is capable of re-solution in pure water. Antipneumococcus and similar antibacterial serums have been extracted from the euglobulin, which is precipitated at 28 to 33 per cent saturation and requires water plus the salt for re-solution.

The more recent classification of blood proteins by electrophoresis as introduced by Tiselius has stimulated further advances. This method lists proteins according to their rate of migration through a U tube while under the influence of an electric current and offers no exact comparison to the results obtained by precipitation with ammonium sulfate. Thus Svensson<sup>4</sup> could demonstrate no electrochemical difference between pseudoglobulin and euglobulin. Albumin moves most rapidly and also has the smallest molecular weight and the greatest osmotic pressure. It is followed by the progressively slower alpha, beta and gamma globulins with decreasing osmotic pressures and increasing molecular weights.

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1 Huntoon, F. M. Pneumococcus Antibody Solution, *J. Lab. & Clin. Med.* **11** 759-762 (May) 1926.

2 Olitzki, L., and Frankel, M. Absorption and Elution of Antibodies from Various Antisera, *Proc. Soc. Exper. Biol. & Med.* **28** 492-494 (Feb.) 1931. Frankel, M. Method of Separating Antibodies from Serum Proteins. Investigation on Protein-Free Antibody, *Proc. Roy. Soc., London, s. B* **111** 165-174 (July 1) 1932.

3 Felton, L. D. Pneumococcus Antibodies—What Are They? *Science* **79** 277-279 (March 23) 1934.

4 Svensson, H. Fractionation of Serum with Ammonium Sulfate and Water Dialysis Studied by Electrophoresis, *J. Biol. Chem.* **139** 805-815 (June) 1941.



Kabat<sup>5</sup> observed that in the horse, cow and pig antibody molecules are extremely heavy, having molecular weights of about 990,000. In the human subject, the monkey and the rabbit, antibody molecules were of regular gamma globulin weight. In certain horses after long immunization he observed smaller antibodies of lesser weight which appeared among the heavier molecules. Kekwick<sup>6</sup> discovered that both beta and gamma globulins contained antitoxic molecules. Antitetanic serum held about 50 per cent in the gamma fraction, Anti-Clostridium-welchii serum 25 per cent and antidiphtheritic serum about 10 per cent. In antipneumococcus serum a new T fraction moving between beta and gamma globulins has been described as the location of the antibodies. Van der Scheer, Wyckoff and Clarke<sup>7</sup> found this true in some instances, while in other animals the gamma fraction contained the increased protective substances. Van der Scheer, Lagsdin and Wyckoff<sup>8</sup> in a later communication reported that antibody activity occurred only in the gamma globulin, with one exception. In this instance blood from a newly immunized horse contained antibodies in fraction T' intermediate between T globulin and gamma globulin. They suggest that with prolonged immunization this fraction might not persist.

Pappenheimer, Lundgren and Williams<sup>9</sup> found the molecular weight of diphtheria toxin to be 70,000 and of the antitoxin 150,000.

Marrack<sup>10</sup> summarized the work of numerous workers to report other observations on the dimensions, shape and actions of antibodies. Some of these observations are unverified, and a few are contradictory.

Rosenau<sup>11</sup> stated of antibodies that "They are not necessarily 'bodies' but may be colloidal or physical states of the blood or other body fluids."

Little of a positive nature is known regarding the site and mode of origin of antibodies. Certain theorists hold that they develop in the fixed cells of the body and are then poured out into the blood and lymph. The lymph glands, the spleen and the reticuloendothelial system have been variously named as the place where production occurs, but convincing evidence is lacking in almost every instance. Sabin<sup>12</sup> stated the modern concept from this viewpoint. It is to be noted that certain of her conclusions are inferred rather than taken as proved facts. Cannon<sup>13</sup> also assumed that antibodies arise in the fixed cells of the reticuloendothelial system. Others have maintained the so-called humoral theory, i. e. that antibodies are formed in the blood and that the circulatory system is the reservoir. Ehrlich's

5 Kabat, E. A. The Molecular Weight of Antibodies, *J. Exper. Med.* **69** 103-118 (Jan) 1939.

6 Kekwick, R. A. Constitution of Some Antitoxic Horse Sera, *Chem. & Indust.* **60** 486 (June 28) 1941.

7 van der Scheer, J., Wyckoff, R. W. G., and Clarke, F. H. Electrophoretic Analysis of Several Hyperimmune Horse Sera, *J. Immunol.* **39** 65-71 (July) 1940.

8 van der Scheer, J., Lagsdin, J. B., and Wyckoff, R. W. G. Electrophoretic and Ultracentrifugal Analysis of Antipneumococcal Horse Sera, *J. Immunol.* **41** 209-223 (June) 1941.

9 Pappenheimer, A. M., Lundgren, H. P., and Williams, J. W. Studies on the Molecular Weight of Diphtheria Toxin, Antitoxin and Their Reaction Products, *J. Exper. Med.* **71** 247-262 (Feb) 1940.

10 Marrack, J. R. Immunochemistry, in Luck, J. M. *Annual Review of Biochemistry*, Stanford University, Calif., Stanford University Press, 1942, vol. 11, pp. 629-654.

11 Rosenau, M. J. *Preventive Medicine and Hygiene*, ed. 6, New York, D. Appleton-Century Company, Inc., 1935, p. 643.

12 Sabin, F. R. Cellular Reactions to a Dye-Protein with a Concept of the Mechanism of Antibody Formation, *J. Exper. Med.* **70** 67-82 (July) 1939.

13 Cannon, P. R. Antibodies and the Protein Reserves, *J. Immunol.* **44** 107-114 (June) 1942.

theory sought to explain the process as an intracellular development but has been practically discarded as inadequate to explain the known facts. Many terms introduced by Ehrlich, however, are still in use. It may well be that antibodies of different classifications arise from different sources.

Concerning specificity, there is no doubt whatever that many immune serums neutralize one specific antigen and no others. Diphtheria antitoxin, first prepared by von Behring, is the prototype. Antipneumococcus serum is to be listed here and is specific for the polysaccharide hapten groups found in the pneumococcus. Heidelberger<sup>14</sup> has discussed these quite fully. Antimeningococcus and other serums may also be listed. It is to be noted that specific antibodies of these types are frequently absent in human beings and animals who have not been exposed to the corresponding infection.

To produce active immunity or therapeutic serum it is usually necessary to stimulate the biologic production by repeated injections of antigen over a period of weeks and often months. Even the results from single doses of alum-precipitated toxoid, the newest and most approved form of immunization to diphtheria, require six weeks or more to mature. The mechanisms responsible seem to be definitely specific and require a lengthy period in which to act. When undeveloped they are powerless in the face of sudden overwhelming attack.

There is, however, a different series of protective reactions which comes into activity whenever any infection gains a foothold and in certain noninfectious conditions. This is the familiar sequence of fever and increase of the white cells of the blood, which can and does become operative within a few hours after the onset of infection. It occurs in a wide variety of diseases of bacterial origin, in diphtheria, pneumonia and epidemic meningitis, all of which have been listed as amenable to treatment by specific antisera, and in addition, in influenza, the acute exanthems and various streptococcal and staphylococcal infections, as well as in the great epidemic diseases Asiatic cholera and plague. Typhoid, typhus and yellow fevers show the thermal change but present irregularities in the action of the white blood cells.

Bacterial infection is also followed by certain chemical changes which have not been thoroughly understood. First, there is an increased metabolism of protein, which, if the end products are not properly eliminated, may produce a striking rise in the nonprotein nitrogen bodies of the blood. This has been noted by Tileston and Comfort,<sup>15</sup> Wakeman and Morrell,<sup>16</sup> Guyer and Lepkovsky,<sup>17</sup> Linton<sup>18</sup> and others. Second, there occurs a shift in the ratio of the blood proteins to one another. The fibrinogen and globulin increase, and the albumin diminishes, with a resultant decrease in the total protein, which produces definite alterations in the albumin-globulin and globulin-fibrinogen ratios. This has been

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14 Heidelberger, M. Immunochemistry, in Luck, J. M. Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1935, vol. 4, pp. 569-586.

15 Tileston, W., and Comfort, C. W., Jr. The Total Non-Protein Nitrogen and the Urea of the Blood in Health and Disease as Estimated by Folin's Method, Arch. Int. Med. **14** 620-649 (Nov.) 1914.

16 Wakeman, A. M., and Morrell, C. A. Chemistry and Metabolism in Experimental Yellow Fever in Macacus Rhesus Monkeys. Concentration of Nonprotein Nitrogenous Constituents in Experimental Yellow Fever in Macacus Rhesus Monkeys, Arch. Int. Med. **46** 290-305 (Aug.) 1930.

17 Guyer, M. F., and Lepkovsky, S. Immunization and the Nitrogenous Constituents of the Blood, J. Immunol. **16** 175-208 (March) 1929.

18 Linton, R. W. Blood Chemical Changes in Experimental Streptococcus Septicemia. J. Exper. Med. **54** 223-231 (Aug.) 1931.

commented on by Hurwitz and Meyer,<sup>19</sup> Hurwitz and Whipple,<sup>20</sup> Wiener and Wiener,<sup>21</sup> Lovett,<sup>22</sup> Rowe,<sup>23</sup> Schoch,<sup>24</sup> Starlinger<sup>25</sup> and others

These phenomena of fever, leukocytosis, changes in the nonprotein nitrogen content of the blood and protein alteration are purely nonspecific and appear in many infections. After a few hours or days soluble immune bodies appear in the blood, and if they are sufficiently potent, recovery with eradication of the infection may be anticipated. The crisis of pneumonia, the lysis of typhoid and other phenomena of recovery are due, at least in part, to those antibodies, whose presence may be proved by appropriate serologic and biologic methods but of whose nature and point of origin nothing is known. They are considered to be an important factor in native or natural immunity.

It is now necessary to make a seeming digression to certain purely experimental data. Balcar, Sansum and Woodyatt<sup>26</sup> found that by the intravenous injection of a concentrated solution of dextrose or sodium chloride into experimental animals, a diuresis could be caused which in a few hours eliminated fluid greatly in excess of that injected. When the output of fluid exceeded the intake by 25 cc or more per kilogram of body weight there occurred a substantial rise in the body temperature, often accompanied by a chill. On the basis of these facts they proposed a so-called dehydration theory of fever according to which the water content of the body was considered to exist in two different states of colloidal combination: first, "free" or uncombined, in which condition it was available to absorb and transport heat to the skin for radiation, to act as a solvent and to perform other functions and, second, "bound" as a hydrate in various organs and tissues of the body, a physicochemical state which prevented its usefulness as a solvent and a vehicle for heat transportation. They conceived of infection as a process which greatly increased the hydration capacity of the body colloids and enabled them to combine with a major portion of the "free" water. The resulting shortage, which prevented absorption and transportation of heat energy, they held responsible for the appearance of fever. That there are increased demands for water during severe febrile illness is shown clinically by the insatiable thirst of the patient and the increased volume of fluid eliminated through the sweat and urine when recovery has come and it is no longer needed. Experimentally many observers have found concentration of the blood and other body fluids during fever.

19 Hurwitz, S. H., and Meyer, K. F. The Serum-Globulins in Infection and Immunity, *J. Exper. Med.* **24** 515-546 (Nov.) 1916

20 Hurwitz, S. H., and Whipple, G. The Albumin-Globulin Ratio in Experimental Intoxications and Infection, *J. Exper. Med.* **25** 231-253 (Feb.) 1917

21 Wiener, H. J., and Wiener, R. E. Plasma Proteins, *Arch. Int. Med.* **46** 236-265 (Aug.) 1930

22 Lovett, B. R. Quantitative Relation of Serum Albumin and Globulin, *Arch. Path.* **4** 984-1024 (Dec.) 1927

23 Rowe, A. H. Albumin and Globulin Content of Human Blood Serum, *Arch. Int. Med.* **18** 455-473 (Oct.) 1916

24 Schoch, A. Ueber Eiweiss-schwankungen im Blutserum bei akuten Infektionskrankheiten, *Schweiz. med. Wchnschr.* **56** 1017-1022 (Oct. 23) 1926

25 Starlinger, W. Ueber das Verhalten der zirkulierenden Eiweisskörper des menschlichen Plasmas unter normalen und krankhaften Bedingungen, *Deutsche med. Wchnschr.* **54** 731-733 (May 4) 1928

26 Balcar, J. O., Sansum, W. D., and Woodyatt, R. T. Fever and the Water Reserve of the Body, *Arch. Int. Med.* **24** 116-128 (July) 1919

My associates and I,<sup>27</sup> having occasion to repeat certain of these experiments found that dehydration caused an increase of protein catabolism and an abnormally large accumulation of nitrogenous debris in the blood of the laboratory animals. It was then necessary to add to the dehydration theory that shortage of water causes a retention of the waste nitrogen, with the development of blood concentrations which sometimes rise to uremic heights. Such heat as is produced at this time is subject to the influences discussed by Balcar, Sansum and Woodyatt.

It was later shown<sup>28</sup> that in animals subjected to dehydration there occurred a rise of the leukocytes similar to that observed in infection.

The point toward which this discussion of somewhat parallel clinical and experimental observations has been directed, and the reason for the preparation of this paper has now been reached. It may be stated thus: Infection generates a biologic reaction which includes (1) fever, (2) leukocytes, (3) changes in the rate of protein disintegration and the levels of waste nitrogen accumulation in the blood, (4) alteration in plasma protein ratios, and (5) the formation of soluble immune bodies. Is it possible, then, that dehydration, which may bring about the first three conditions, is also responsible for the fourth and could be used as a method for production of the fifth? In other words, is it possible to use this method to change the preparation of immune serums from a biologic to a physiochemical problem and so to remove it from the animal body into the test tube?

I<sup>29</sup> have called attention to effects often obtained by the treatment of severe infections with blood transfusion wherein fresh compatible blood seemed to carry certain raw materials into the patient's blood stream. These raw materials appeared, after due intravital processing, to emerge as antibodies which exerted a favorable influence on the course of the disease. Proof that such a change actually takes place would lend strength to the claims advanced by the advocates of the humoral theory of immunity. If the transformation could be reproduced under proper control in the chemical laboratory, such an introduction of new methods into the study of immune phenomena might conceivably result in definite advances in therapy.

Recent developments suggest that production of antibodies under laboratory conditions is already within our grasp. In the early days of the century Moll<sup>30</sup> attempted to convert albumin into globulin by treatment with gentle heat and alkalis and found certain globulin-like properties in the product. His critics, however, pointed out that the amino acid composition was not correct, and the procedure soon ceased to have interest. Today it would be said that he had produced a denaturation of the protein.

Recently Pauling and Campbell<sup>31</sup> published an epoch-making report. They studied the results of denaturation of protein in the presence of an antigen and found that it opens the way to the preparation, *in vitro*, of specific antiserums. Using purified globulin, they observed that treatment with alkalis in varying concentrations up to  $p_H$  11.0 caused the protein molecules to "uncoil" and take

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27 Bacon, D. K., Anslow, R. E., and Eppler, H. H. Intestinal Obstruction, *Arch. Surg.* **3** 641-654 (Nov.) 1921.

28 Bacon, D. K., Novy, F. O., and Eppler, H. H. Factors in Leukocytosis, *Arch. Int. Med.* **30** 229-239 (Aug.) 1922.

29 Bacon, D. K. Blood Transfusion in the Treatment of Sepsis, *Minnesota Med.* **18** 30-34 (Jan.) 1935.

30 Moll, L. Ueber kunstliche Umwandlung von Albumin in Globulin, *Beitr. z. chem. Phys. u. Path.* **4** 563-577, 1903.

31 Pauling, L., and Campbell, D. H. The Manufacture of Antibodies *in Vitro*, *J. Exper. Med.* **76** 211-220 (Aug.) 1942.

the imprint of various dyestuff antigens. After renaturation by restoration of a normal  $p_H$  value there remains a configuration of the globulin molecule which enables it to combine with the antigen and act to neutralize it. Similarly, using heat denaturation, at a temperature of 57 C, they have prepared antibodies specific to pneumococcus polysaccharide which will after renaturation precipitate further increments of the polysaccharide. Thus the flexibility of the globulin molecule is advanced as a prime factor in combating various bacterial poisons, and denaturation, at least of some types, is shown not as a laboratory curiosity but as a dynamic force which is of vital importance in the maintenance of health and life.

Pauling and Campbell have carried out denaturation under artificial conditions which are seemingly incompatible with life, such as a  $p_H$  of 11.0 or a temperature of 57 C. I have sought to use procedures which can more easily be visualized as acting in the living body on whole blood plasma where natural immunity is found rather than in a dilute solution of purified globulin.

If the previously mentioned dehydration theory has any merit, blood protein must be thought of as consisting of a bound water fraction closely united to the protein molecule and perhaps within the molecular framework, the water of hydration, and a free or solvent fraction which carries the body electrolytes, such as chlorides, sulfates and bicarbonates. If any process should cause a decrease in the free water while the mineral content remained constant, one might expect a rise in the concentration of salts and also, since a  $p_H$  of 7.00 is regarded as neutral and the average  $p_H$  of blood plasma is about 7.4, it seems probable that the excess alkalinity of  $p_H$  0.4 would become concentrated in the diminishing solvent fluid and give rise to an increase of hydroxyl ion concentration and an abnormally high  $p_H$  value in this fraction.

#### EXPERIMENTAL DATA

Experimental work was undertaken to test this theory. Citrated beef blood was obtained through Swift and Company at South St. Paul. It contained sulfanilamide as a preservative. It was separated by centrifugation, and the clear plasma was obtained. The  $p_H$  values were immediately determined by electrometric readings. Since no precautions were taken to prevent the escape of carbon dioxide values ranged from  $p_H$  7.45 to  $p_H$  7.58, which is a trifle more alkaline than the average reading on blood collected under oil to retain the gas.

The plasma was then subjected to dehydration by the method of Flosdorf and Mudd<sup>32</sup>. The apparatus consists, in essence, of a closed flask containing plasma, a cold chamber surrounded by solid carbon dioxide to collect the fluid which is withdrawn and a vacuum pump to exhaust the system and extract water from the plasma. The entire system is connected by pressure-resistant tubing. It is a method commonly used to dry and preserve plasma for later use in transfusion. While Flosdorf and Mudd have devised later methods with different agents for absorption of the extracted water which are used for mass production of dried plasma, the original method proved satisfactory for the purpose of this study. Methods which require the spraying of plasma into a heated vacuum chamber were considered unsuitable and were not employed.

When the pump is first started, the air is rapidly exhausted from the plasma flask, and a violent boiling of the contents results. At this point it is necessary to admit small amounts of air to prevent entrance of the foam into the tubing. After a few minutes, when the dissolved gases, such as carbon dioxide and oxygen

<sup>32</sup> Flosdorf, E. W., and Mudd, S. Procedure and Apparatus for Preservation in "Lyophile" Form of Serum and Other Biological Substances, *J. Immunol.* **29**: 389-425 (Nov.) 1935.

have been extracted and the heavier water vapor begins to pass over, the process becomes much more quiet and may be left to progress to completion with little further attention

This process was carried out on a number of samples of plasma to note the effect of dehydration. Estimations of the  $p_H$  were made before starting and were repeated at the end of the violent boiling period, which consumes about ten minutes, in order to note the effect of the withdrawal of carbon dioxide. A third estimation was made after about fourteen hours, when the fluid was almost dry but still mushy enough to make a good contact with the glass electrode. The last values, of course, would be slightly less than the value for dry plasma, which cannot be easily taken. The readings are given in the accompanying table.

Reference to this table will show that dehydration causes a considerable rise in the alkalinity of plasma. True, this has not been observed in the blood of living animals, but if electrodes could be fashioned to take readings in the ultramicroscopic free water fractions of plasma and not be influenced by the neighboring bound water molecules, increased alkalinity might be found. It would be a condition of great

*Results of Dehydration on  $p_H$  of Blood Plasma*

Specimen	1 $p_H$ Before Treatment	2 $p_H$ After 10 Minutes	3 $p_H$ at Near Dryness
1	7.52	7.64	8.54
2	7.55	7.68	8.70
3	7.45	7.60	8.45
4	7.58	7.72	9.10
5	7.50	7.68	8.32
6	7.48	7.62	8.65
7	7.50	7.65	8.50
8	7.55	7.74	8.42
9	7.54	7.70	8.54
10	7.48	7.68	7.95

It is to be noted that all values in column 3 were taken on incomplete dehydrated plasma which was still mushy enough to make a good contact with the glass electrode. The  $p_H$  of completely dried plasma would probably be 0.2 to 0.5 greater.

internal chemical stresses with sharply contrasting concentrations in physically adjacent particles. This will be commented on later.

Further specimens of plasma were dehydrated as has been described and during the process were treated with an antigen. In these experiments the flask containing the specimen was placed in the incubator with the tube connection to the vapor trap entering through the upper vent hole. This attempt to maintain body temperature was unsuccessful because of the rapid withdrawal of heat in the vaporization process, and the flask remained decidedly cold during the entire period. Consequently, after the contents were about 90 per cent dehydrated and resembled a thick, mushy syrup, the suction was removed and the air pressure in the flask was permitted to return to normal. It was then kept in the incubator for an additional twelve hours to permit completion of any chemical adjustment.

#### METHOD

One hundred cubic centimeters of clear citrated and centrifuged beef plasma was placed in a 1,000 cc Erlenmeyer flask. This was fitted with a rubber stopper and connected by rigid rubber tubing to a vapor trap containing solid carbon dioxide and thence to a vacuum pump. The pump was started and allowed to run for ten to fifteen minutes with occasional small admissions of air until active foaming of the plasma had subsided. The flask was then opened and 2 cc of staphylococcus toxin added. The container was then shaken to insure thorough mixing. The toxin, obtained from the Lederle Laboratories, Inc., their no. 307H565, was stated to contain 12,000 dermonecrotic doses per cubic centimeter. The cork was replaced and the pump again started and continued for twelve to fourteen hours until near dryness.

was reached. During this time the flask was agitated at intervals to assist uniform evaporation and prevent caking around the edges. The pump was then disconnected, and the atmospheric pressure in the flask was permitted to return to normal. It remained in the incubator another twelve hours.

After this sufficient distilled water was added to restore the plasma to its original volume, and both the control and the processed specimens were adjusted to  $pH$  7.4 with tenth-normal acetic acid. This is important, as the processed specimen is apt to be definitely alkaline in spite of the fact that no alkali has been added. It was filtered and 5 cc pipetted into each of two test tubes, 5 cc of unprocessed plasma from the same blood was placed in a third tube for a control, 0.5 cc of staphylococcus toxin each was added to one processed tube and the control tube, diphtheria toxin obtained from the Minnesota State Board of Health was placed in the second processed tube as another control, 0.5 cc being used. The three tubes were set in the incubator for twelve hours to facilitate any change that might occur. A series of such experiments was made.

A second series was carried out in which plasma was dehydrated with diphtheria toxin as an antigen and test tubes were set up containing diphtheria toxin in the unprocessed control and one tube of processed plasma. Staphylococcus toxin in the second processed tube gave another control.

#### RESULTS

In the series which had been dehydrated against staphylococcus toxin, tube 1, containing additional toxin from the same lot, in every instance gave a copious precipitate which after settling filled about 12 to 15 per cent of the test tube. This was presumably antigen-antibody precipitate. In the two control tubes the results were strikingly different. In many instances no precipitate at all came down while in several there was an amount just sufficient to cover the bottom of the tube after settling. There was never any question or confusion, and in every instance the processed plasma treated with homologous toxin was strikingly different from the two controls.

In the series dehydrated against diphtheria toxin, tube 1, containing a further increment of the same toxin, showed a similar but less profuse precipitate than in the staphylococcus series. About 5 to 6 per cent of the volume of the tube was occupied by antigen-antibody precipitate, while in the control tubes the results were similar to those obtained with the controls in the previous series. There was usually no precipitate, except in 2 or 3 instances in which there was a very small amount, which, however, could not be confused with that which appeared in the processed tube treated with homologous toxin. Results in this series were definite without being as spectacular as those noted in the staphylococcus series. Results may be illustrated in tabular form as follows:

Plasma Dehydrated with Staphylococcus Antigen		
Control 1	Control 2	Test
Unprocessed plasma plus staphylococcus toxin	Processed plasma plus diphtheria toxin	Processed plasma plus staphylococcus toxin
Precipitate — to $\pm$	— to $\pm$	++++
Plasma Dehydrated with Diphtheria Antigen		
Control 1	Control 2	Test
Unprocessed plasma plus diphtheria toxin	Processed plasma plus staphylococcus toxin	Processed plasma plus diphtheria toxin
Precipitate — to $\pm$	— to $\pm$	++

It will be seen that these results are comparable to the ones obtained by Pauling and Campbell and show specific precipitates obtained by the treatment of plasma which had gone through a dehydration process in the presence of an antigen with further increments of the same antigen. The faint precipitate which appeared in the control tubes in a few instances could represent preexisting antibodies acquired during the life of the animal.



## COMMENT

It is possible that several different forms of immunity exist, and they may arise from as many different sources. This report deals only with the specific antibodies of the blood globulin. There may be nonspecific protective substances here in addition to the specific ones, as Street<sup>33</sup> and van der Scheer, Bohnel, Clarke and Wyckoff<sup>34</sup> have demonstrated. If so, the work of separation and classification has scarcely begun. These specific antibodies seem to be of a protective nature, and the ability to combine with and carry down antigen may identify them as precipitins. The fact that the concentration of agglutinins, in the experience of many workers, fluctuates entirely independently of curative antibody strength undoubtedly places the two in separate categories. Opsonins occupy still another niche, and according to Wright<sup>35</sup> their entire functional activity is in doubt.

To return to the subject of this research, evidence is offered that antibodies can be formed in the native blood plasma by methods available in the average well equipped chemical laboratory and entirely independently of any mysterious "body reaction." These methods, although carried out *in vitro*, approximate the chemical forces which act in the body.

At this point it will be objected that evaporation of plasma in a flask and under reduced pressure to a state of near-dryness can have little in common with any conditions which exist in the circulating blood of a living animal having a free respiratory exchange under normal atmospheric pressure. It is true that differences in degree may exist between the experimental conditions just described and the changes which are found clinically, but on closer scrutiny the differences in kind seem less final than at first glance. A reduction in the volume of free water with its solvent action concentrates the dissolved electrolytes regardless of the disposition of the fraction removed. In this instance, chemical segregation in a bound water system should have no basic difference in effect from that exerted by loss through evaporation. The free water fraction is reduced in volume and contains an increased concentration of electrolytes in either case.

In glass, this causes a considerable rise in the alkalinity of the plasma. *In vivo*, no alkalinity comparable with these experimental figures has ever been observed.

While life lasts, the body, by variations in the carbon dioxide tension and the action of the various buffer salts, maintains a  $p_H$  value in the blood which rarely reaches 7.55. It seems not impossible, however, that this value is deceptive and that plasma actually has no homogeneous and uniform hydrogen ion concentration but has instead two different values representing bound and free water molecules in which our indicators or electrode systems read the mean. In health the two different values should not be far apart but should form a sensitive mechanism ready to respond to antigenic stimulation with a swelling of the protein molecule due to an increase in the amount of bound water and a decrease in the amount of free water with a rise in alkalinity, or masked alkalosis. This would produce a tension at the interfacial surfaces which might conceivably alter the form or consistency of the protein sufficiently to permit its adaptation to the contours of the antigen molecule. The result would be the formation of antibodies. After recovery and restoration of a state of normal hydration there should be a disappearance of

33 Street, J. A. Studies on the Mechanism of Species Specific Immunity Against Pneumococcus Infection, *J. Immunol.* **44** 53-69 (May) 1942.

34 van der Scheer, J., Bohnel, E., Clarke, F. H., and Wyckoff, R. W. G. An Electrophoretic Examination of Several Antipneumococcal Rabbit Sera, *J. Immunol.* **44** 165-174 (June) 1942.

35 Wright, A. E. On the Need for Abandoning Much in Immunology That Has Been Regarded as Assured, *Proc. Roy. Soc. Med.* **35** 161-186 (Jan.) 1942.



the masked alkalosis and a rapid sweeping of the excess waste nitrogen through the kidneys, the new antibodies being left as sole evidence of the strain that had existed.

In order to have a more complete understanding of the processes involved in the production of fever and the development of immunity, it is necessary to begin with the work of Balcar, Sansum and Woodyatt,<sup>36</sup> which has already been mentioned. Since they first advanced their hypothesis of "free" and "bound" water it has attracted the interest of the biochemical world, and much time and ingenuity have been expended on investigations of the question. Gortner,<sup>36</sup> who independently conceived the same varying relation of water to protein, discussed the evidence at some length, and showed clearly that such a dual status of water actually exists in many vegetable proteins and in certain other nonprotein colloidal systems as well. Opinions regarding the status of water in animal protein and particularly in blood are not unanimous. Jochims<sup>37</sup> and others affirmed the existence of bound water, while Sunderman<sup>38</sup> and Greenberg and Greenberg<sup>39</sup> denied it. The results of their experimental work have since been challenged on technical grounds. Robinson and Parsons<sup>40</sup> found much water present in blood and muscle which, since it was not frozen at  $-20^{\circ}\text{C}$  must have been bound water, Hayasida,<sup>41</sup> in measuring the "nonsolvent" space of blood serum, discovered that it occupies about 20 volumes per cent, with rather wide fluctuations occurring as the salt content varies, and gave added proof from a different viewpoint. There is, in addition, evidence of adsorption or binding of the chloride ion in the protein molecule, a state presumably not one of solution but one which permits the protein to come into intimate contact with the bound ion. He also called attention to the fact that exclusion of a portion of the fluid from functioning as a solvent results in a greater condensation of electrolytes in the remainder than would be evident if it were calculated as a uniform concentration in the entire volume. Sunderman and Austin,<sup>42</sup> also Rackemann, Longcope and Peters<sup>43</sup> have shown clinically that febrile disease is accompanied by retention of water, a phenomenon which suggests some alteration of the structures and tissues.

It seems reasonable to believe that when infection is present dehydration, alkalinization and remodeling of globulin proceed as long as it persists or as long as the forms from which it can be derived are in existence. Cannon's<sup>13</sup> insistence on a plentiful supply of protein raw material to feed the chemical "templates" of the reticuloendothelial system applies with equal urgency to the blood stream and the antibodies which originate there. Exhaustion of the proper native proteins results

36 Gortner, R. A. The Role of Water in Protoplasm, in Luck, J. M. Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1932, vol. 1, pp. 21-50, Water in Its Biochemical Relationships, *ibid*, 1934, vol. 3, pp. 1-19.

37 Jochims, J. Viscosimetrische Untersuchungen über die Wasserbindung der Plasmakolloide, die Wasserbindung der Eiweisskörper in normalen Blutplasma, *Arch f d ges Physiol* **230** 255-262, 1932.

38 Sunderman, F. W. The Osmotic Behavior of Water of Blood Serum, *J Biol Chem* **96** 271-283 (April) 1932.

39 Greenberg, D. M., and Greenberg, M. M. Ultrafiltration II "Bound" Water (Hydration) of Biological Colloids, *J Gen Physiol* **16** 559-569 (March) 1933.

40 Robinson, W., and Parsons, E. Hemorrhage and "Shock" in Traumatized Limbs, *Arch Path* **12** 869-888 (Dec.) 1931.

41 Hayasida, A. The "Non-Solvent Space" of the Serum and the Chlorine Bound by the Serum Protein, *J Biochem* **18** 107-124 (July) 1933.

42 Sunderman, F. W., and Austin, J. H. Studies of Serum Electrolytes VI Water Metabolism in Pneumonia, *Am J M Sc* **179** 167-176 (Feb.) 1930.

43 Rackemann, F. M., Longcope, W. T., and Peters, J. P. The Excretion of Chlorides and Water and the Renal Function in Serum Disease, *Tr A Am Physicians* **31** 215-224, 1916.

in a collapse of resistance, which may be averted by blood transfusion or by injection of the proper grade of antiserum. The sulfonamide compounds have of recent years proved a powerful complement to natural immunity. Either without the other may fail, but both together have a remarkable curative record.

The globulin molecule is, in general, much bulkier than the albumin molecule and has a lower colloidal osmotic pressure and a lower solubility. It has been shown that globulin has a molecular weight roughly twice or some other multiple of that possessed by albumin, and it seems not impossible that the increase of globulin represents a joining or polymerization process of the albumin molecules. Schmidt<sup>44</sup> and Astbury, Dickinson and Bailey<sup>45</sup> discuss molecular weights and polymerization of proteins. The writings of Cohn and his associates<sup>46</sup> carry the same thought. They stated "Actually most globulins have molecular weights of from 140,000 to 170,000, being about twice as large as the albumins, whose molecular weight is in the neighborhood of 73,000. A small proportion of the globulin has the still higher molecular weight of about 900,000, or about twelve times as large as the albumin, and globulin of even larger molecular weight has been observed."

The increase in the nonprotein nitrogen content of the blood *in vivo* seems to be directly caused by dehydration, which prevents urinary excretion without delaying the progressive accumulation of metabolic nitrogen. This includes, of course, a concentration of the blood as described by Barbour and Gilman,<sup>47</sup> since halving of the volume gives double the concentration of nonprotein nitrogen. *In vitro*, plasma which has been dried in a vacuum and redissolved in distilled water to the original volume shows an unchanged nitrogen concentration. If it is restored to half its original volume the concentration of nitrogen is doubled. At times of increased concentration there may also be an increment derived from the cells as described by Bellis and Scott.<sup>48</sup>

The foregoing explanation is of course highly speculative and at present impossible to prove. However, it represents an attempt to group together in their proper relationship certain phenomena which arise as a result of infection and are presumably an integrated and orderly process not isolated events having no bearing on one another.

The suggestion that the more complex proteins are derived from the simpler ones may reopen a controversy which has existed since the early days of the century when Moll<sup>30</sup> attempted to convert albumin into globulin by treatment with gentle heat and alkalis and believed that he had succeeded. His results and interpretation have been largely rejected. Other attempts to form globulin have been made at intervals. A more recent one is that of Fischer,<sup>49</sup> who treated albumin with heparin

44 Schmidt, C. L. A. *Chemistry of the Amino-Acids and Proteins*, in Luck, J. M. *Annual Review of Biochemistry*, Stanford University, Calif., Stanford University Press, 1932, vol. 1, pp. 151-166; *The Chemistry of the Amino Acids and Proteins*, *ibid.*, 1933, vol. 2, pp. 71-91.

45 Astbury, W. F., Dickinson, L., and Bailey, K. *The X-Ray Interpretation of Denaturation and the Structure of the Seed Globulins*, *Biochem. J.* **29**, 2351-2360, 1935.

46 Cohn, E. J., and others. *Properties and Functions of the Purified Proteins of Animal and Human Plasmas*, in Mudd, S., and Thalhimer, W. *Blood Substitutes and Blood Transfusion*, Springfield, Ill., Charles C. Thomas, Publisher, 1942, pp. 173-180.

47 Barbour, H. G., and Gilman, A. *Heat Regulation and Water Exchange*. XVII. *The Relation of Serum Osmotic Pressure to the Onset of Fever*, *J. Pharmacol. & Exper. Therap.* **50**, 277-285 (March) 1934.

48 Bellis, C. J., and Scott, F. H. *The Alteration of Protein Distribution, *in Vitro* Between Corpuscles and Plasma Caused by Isosmotic and Hyperosmotic Solutions*, *J. Biol. Chem.* **111**, 17-42 (Sept.) 1935.

49 Fischer, A. *Transformation de la serumalbumine en serumglobuline*, *Compt. rend. Soc. de biol.* **108**, 882-883 (Dec. 4) 1931.

(antipiothrombin) and concluded that the transformation occurred. Hooker and Boyd<sup>50</sup> disagreed, and at this writing it may be said that the burden of proof rests on those who believe the conversion possible. In his electrophoretic studies Scudder<sup>51</sup> observed that during the preparation of dried transfusion plasma an increase of gamma globulin, the fraction which carries immunity, appeared and that the increase was still present when the plasma was redissolved. The gamma globulin originates from one or more of the native proteins, perhaps the albumin and possibly through the agency of polymerization, as has previously been suggested. This is an added reason for the use of whole plasma in the preparation of artificial antibodies. The use of purified globulin requires a previous chemical separation of this protein and also eliminates the other forms which are brought into the gamma globulin picture by dehydration and are then available to increase the yield of finished antibodies.

Block, Darrow and Cary<sup>52</sup> concluded that the separation of blood proteins by physicochemical means is an unnatural one and that the globulins and albumins so obtained are artificial products of the reagents used in their preparation. They discovered, through quantitative studies of the constituent amino acids of the total serum protein, an unchanging ratio of arginine to lysine, both in blood from patients with nephrosis with an albumin-globulin ratio of less than 1 and in normal blood with a far higher ratio. In isolated and supposedly pure proteins this is not so and albumin always gives a larger yield of lysine than does globulin. These observations are evidence that the change is in the state of molecular aggregation rather than intramolecular and are not incompatible with the hypothesis that a polymerization process due to changes in hydration and alkalinity is a cause of protein shift from albumin to globulin which is readily remodeled into antibody protein. The argument over conversion of albumin into globulin is thus reduced to one of no particular immunologic moment. This is perhaps the preferable viewpoint from which to speculate on the exact nature of the changes. Suffice it to say that under the stimulus of dehydration certain of the proteins undergo an alteration of solubility which seems to place them in other groups.

This theory also permits a more detailed explanation of certain nonspecific phases of immunity than has previously been possible. For instance, the intramuscular injection of milk or the intravenous injection of typhoid vaccine is used to cause a reaction which frequently benefits certain types of arthritis. In the past the improvement has usually been attributed to the accompanying leukocytosis and perhaps the increased heat during the period of fever. Now it can be recognized that the changes due to fever include swelling of the protein molecules, reduction of the amount of the free water and an ensuing masked alkalosis. At this juncture much of the gamma globulin is in a plastic or "uncoiled" state, and while some molecules interact with the typhoid or milk antigen others come into contact with the arthritic antigen which lacks the potency to initiate its own reaction, and are molded into a suitable form to neutralize it.

Immunity has up to the present been described as a systemic process confined to the blood stream. It is logical, however, to believe that it may develop wherever proteins akin to those of the blood are found. In various regional and local infections the signs point to the local development of immunity as a method of anti-

50 Hooker, S. B., and Boyd, W. D. Alleged Transformation of Serum Albumin into Serum Globulin, *J. Biol. Chem.* **100** 187-194 (March) 1933.

51 Scudder, J. Studies in Blood Preservation. The Stability of Plasma Proteins, *Ann. Surg.* **112** 502-519 (Oct.) 1940.

52 Block, R. J., Darrow, D. C., and Cary, M. K. Basic Amino Acids of Serum Proteins *J. Biol. Chem.* **104** 347-350 (Feb.) 1934.

bacterial defense. A furuncle, for instance, usually shows in the earlier stages, a small area of redness and pain where the infecting organisms are located. Surrounding this is an area of edema many times larger, which subsides when the infection has been checked and its toxic products neutralized. Drainage and repair of necrotic areas are later developments. The actual furuncular cavity may persist long after immunity is established and the increased water content of the surrounding proteins has vanished. As in the systemic version of the process, leukocytes attracted by the nitrogenous fragments migrate to the center of the disturbance to engulf the offending organisms and form pus. The intercellular lymph closely resembles blood plasma in its chemical characteristics and undoubtedly participates in local immune reactions.

These studies suggest that all preserved blood plasma which has been through a drying process has been subjected to some measure of denaturation and to immunization of an abortive and incomplete type. Scudder<sup>53</sup> has shown by a study of electrophoretic patterns that in plasma dried from a frozen state these changes are minimal, while in liquid or heated plasma they are much greater. If it were considered desirable to prevent the changes and have only the unaltered native proteins, it could perhaps be done by careful control of the  $pH$  range so that it never rose above 7.45 or / 5.

#### SUMMARY AND CONCLUSIONS

Recent discoveries indicate that the production of antibodies under laboratory conditions is within the bounds of possibility. Dehydration has been shown to cause conditions favorable to the necessary changes in the proteins of the plasma. The effect of dehydration and the mechanism by which antibodies are produced in the living organism are discussed.

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<sup>53</sup> Scudder, J., in Mudd, S., and Thalhimer, W. Blood Substitutes and Blood Transfusion, Springfield, Ill., Charles C. Thomas, Publisher, 1942, pp. 126-136.

# THERAPY WITH SULFONAMIDE COMPOUNDS FOR PATIENTS WITH DAMAGE TO THE LIVER

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The presence of damage to the liver is one of the few conditions which are still considered to contraindicate the use of sulfonamide compounds or, at least, to require caution in their administration. Many clinical reports, however, include cases in which these drugs have been successfully used for the treatment of infections in the presence of jaundice of varying intensity and for patients with extensive damage to the liver. Adequate studies of the effects of this form of therapy on the hepatic function in such cases are few. In this paper there is reported a series of 37 patients who presented evidence of acute or chronic damage to the liver and who, for various reasons, received either sulfathiazole or sulfadiazine in full therapeutic doses. In each of these cases some studies were made in an attempt to determine the effect of the sulfonamide therapy on hepatic function.

## LITERATURE

The liver plays an important role in the metabolism of many organic compounds, including sulfanilamide, its derivatives and some related compounds, notably para-aminobenzoic acid<sup>1</sup>. Indeed, the synthesis of hippuric acid from benzoic acid is a useful test of hepatic function<sup>1d</sup>. The acetylation of sulfanilamide and probably of most of its therapeutically active derivatives takes place chiefly in the liver in some experimental animals, such as the cat,<sup>1e</sup> while in others, notably the rabbit, it is probably confined to that organ<sup>1f</sup>. Acetylation in the rabbit liver has also been shown to take place *in vitro*<sup>2</sup>. Scudi and his co-workers<sup>3</sup> demonstrated a definite

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1 (a) Harrow, B., Mazur, A., and Sherwin, C. P. Studies on Acetylation. The Fate of *p*-Aminobenzoic Acid in the Rabbit, *J. Biol. Chem.* **102** 35 (Sept.) 1933. (b) Klein, J. R., and Harris, J. S. The Acetylation of Sulfanilamide *In Vitro*, *ibid.* **124** 613 (Aug.) 1938. (c) Harris, J. S., and Klein, J. R. Acetylation of Sulfanilamide by Liver Tissue *In Vitro*, *Proc. Soc. Exper. Biol. & Med.* **38** 78 (Feb.) 1938. (d) Quick, A. J. The Synthesis of Hippuric Acid. A New Test of Liver Function, *Am. J. M. Sc.* **185** 630 (May) 1933. (e) The Relationship Between Chemical Structure and Physiological Response. The Conjugation of Substituted Benzoic Acids, *J. Biol. Chem.* **96** 83 (April) 1932. (f) Stewart, J. D., Rourke, G. M., and Allen, J. G. Acetylation of Sulfanilamide, *Surgery* **5** 232 (Feb.) 1939. (g) Van Winkle, W., Jr., and Cutting, W. C. Acetylation of Sulfanilamide and Sulfapyridine in the Cat, *J. Pharmacol. & Exper. Therap.* **69** 40 (May) 1940.

2 Klein and Harris<sup>1b</sup>, Harris and Klein<sup>1c</sup>, Van Winkle and Cutting<sup>1g</sup>.

3 (a) Scudi, J. V., Ratish, H. D., and Bullowa, J. G. M. Increased Glycuronate Excretion Following Administration of Sulfapyridine, *Science* **89** 516 (June 2) 1939. (b) Scudi, J. V., and Robinson, H. J. Urinary Excretion of Sulfapyridine in the Rat. A Relationship of the Liver to Urolithiasis, *Am. J. M. Sc.* **201** 711 (May) 1941.

increase in excretion of glucuronic acid during administration of sulfapyridine and concluded that a large part of the "free" drug<sup>4</sup> may really be present in the urine in the form of the highly soluble glucuronate. Sulfanilamide failed to stimulate the output of glucuronic acid, while sulfathiazole did so to a moderate extent. In rats with the liver damaged by phosphorus, the increase in output of glucuronic acid did not occur when sulfapyridine was given, and there was a marked increase in urolithiasis.

There is now considerable evidence that the sulfonamide compounds may produce appreciable damage to the liver in experimental animals and also in man. The frequency and extent of this injury varies with the different derivatives. The available information concerning each of the commonly used sulfonamide compounds will therefore be considered separately.

Sulfanilamide is generally considered to be more injurious to the liver in human therapy than are the other widely used derivatives, but this has not been true in all studies on experimental animals. In rats after prolonged administration of sulfanilamide, Davis, Harris and Schmeisser<sup>5</sup> demonstrated diffuse degeneration of the hepatic parenchyma with focal necrosis and regeneration of cells as evidenced by mitosis. Kiems, Martin and Dille<sup>6</sup> also observed increased consumption of oxygen *in vitro* by the livers of rats which had been subjected to repeated administration of sulfanilamide.

On the other hand, Molitor and Robinson<sup>7</sup> found no evidence of damage to the liver in dogs after prolonged administration of sulfanilamide in large doses. In the livers of rats similarly treated histologic studies revealed nothing significant except some degenerative changes. Greisheimer and her co-workers<sup>8</sup> could not demonstrate any appreciable change in blood sugar or in formation or storage of glycogen after the administration of sulfanilamide in single or repeated doses. Furthermore, there is evidence that the frequency and degree of damage to the liver resulting from carbon tetrachloride poisoning are actually less when sulfanilamide is given at the same time.<sup>9</sup> This protective action of sulfanilamide is not inhibited by paraaminobenzoic acid.<sup>9a</sup> When sulfanilamide is given after the damage from carbon tetrachloride has occurred, it does not interfere with healing.<sup>9a</sup> In animals with obstructive jaundice produced by ligation of the common bile duct no additional damage due to administration of sulfanilamide was discerned. This drug also seems to protect rats from the damage to the liver caused by alcohol.<sup>9c</sup> These findings

4 Marshall, E. K., Jr., and Litchfield, J. T., Jr. Determination of Sulfanilamide, *Science* **88** 85 (July 22) 1938.

5 Davis, H. A., Harris, L. C., Jr., and Schmeisser, H. C. Tissue Changes Following Prolonged Administration of Sulfanilamide in Rats, *Arch. Path.* **25** 750 (May) 1938.

6 Kiems, A. D., Martin, A. W., and Dille, J. M. Experimental Study of Tolerance to Sulfanilamide in the Albino Rat, *J. Pharmacol. & Exper. Therap.* **71**:215 (March) 1941.

7 Molitor, H., and Robinson, H. Some Pharmacological and Toxicological Properties of Sulfanilamide and Benzylsulfanilamide, *J. Pharmacol. & Exper. Therap.* **65** 405 (April) 1939.

8 Greisheimer, E. M., Hafkesbring, R., and Magalhães, H. Blood Sugar and Liver Glycogen. I. After Single Doses of Sulfanilamide, Sodium Sulfapyridine, and Sodium Sulfathiazole, *M. Times*, New York **69** 170 (April) 1941. Hafkesbring, R., Greisheimer, E. M., and Wertenberger, G. E. Blood Sugar and Liver Glycogen. II. Recovery After Single and Repeated Doses of Sulfonamide Drugs, *ibid.* **69** 467 (Nov.) 1941.

9 (a) Forbes, J. C., Leach, B. E., and Williams, G. Z. Protective Action of Sulfanilamide Against Liver Cirrhosis from Chronic Poisoning with Carbon Tetrachloride, *Proc. Soc. Exper. Biol. & Med.* **51** 47 (Oct.) 1942. (b) Leach, B. E., and Forbes, J. C. Sulfonamide Drugs as Protective Agents Against Carbon Tetrachloride Poisoning, *ibid.* **48**:361 (Oct.) 1941. (c) Machella, T. E., and Higgins, G. M. The Effect of Sulfanilamide on the Experimentally Damaged Liver, *Am. J. M. Sc.* **204** 194 (Aug.) 1942.

do not necessarily mean that sulfanilamide itself is innocuous to the liver. They suggest, rather, that it may interfere in some way with the action of other toxic agents and reduce the damage done by them.

Since the early clinical reports of Hageman and Blake<sup>10</sup> and Harvey and Janeway,<sup>11</sup> evidence of damage to the liver resulting from administration of sulfanilamide has been presented by a number of observers.<sup>12</sup> Long<sup>12k</sup> found hepatitis with jaundice and impairment of hepatic function in the absence of anemia in 0.6 per cent of patients treated with sulfanilamide. He stated that the prognosis in such cases is good if use of the drug is stopped and fluids are forced. Damage to the liver may appear after a few grams of sulfanilamide has been given, or it may occur only after an extended period of medication. In the 2 cases reported by Spring and Bernstein<sup>12q</sup> there was definite clinical and laboratory evidence of hepatitis after the ingestion of 4.6 Gm. in the one and of 7 Gm. in the other. In other cases damage developed only after prolonged or repeated administration.<sup>13</sup> All grades of damage have been observed, including several instances of acute yellow atrophy, of which

10 Hageman, P. O., and Blake, F. G. A Specific Febrile Reaction to Sulfanilamide Drug Fever, *J. A. M. A.* **109** 642 (Aug. 28) 1937.

11 Harvey, A. M., and Janeway, C. A. The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide (Para-Aminobenzene Sulfonamide), *J. A. M. A.* **109** 12 (July 3) 1937.

12 (a) Bannick, E. G., Brown, A. D., and Foster, F. P. Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds. Further Clinical Observations, *J. A. M. A.* **111** 770 (Aug. 27) 1938. (b) Berger, S. S., and Applebaum, H. S. Toxic Hepatitis Due to Sulfanilamide. Report of a Fatal Case with Histopathologic Findings in the Liver, *J. Lab. & Clin. Med.* **26** 785 (Feb.) 1941. (c) Cantarow, A., and Wirts, C. W. Hyperbilirubinemia Following Administration of Sulfonamides, *ibid.* **28** 71 (Oct.) 1942. (d) Cline, E. W. Acute Yellow Atrophy of the Liver Following Sulfanilamide Medication, *J. A. M. A.* **111** 2384 (Dec. 24) 1938. (e) De Bonis, G. Sull'azione epatotossica dei preparati sulfamidici, *Athena* **9** 248 (Aug.) 1940, abstracted, *J. A. M. A.* **115** 1928 (Nov. 30) 1940. (f) Fitzgibbon, P., and Silver, B. Toxic Necrosis of the Liver Following the Use of Sulfanilamide, *California & West. Med.* **50** 123 (Feb.) 1939. (g) Garvin, C. F. Toxic Hepatitis Due to Sulfanilamide, *J. A. M. A.* **111** 2283 (Dec. 17) 1938. (h) Gertler, W. Leberparenchymschädigung nach Verabreichung von Prontosil bei chronisch rezidivierendem Erysipel, *Dermat. Wehnschr.* **106** 725 (June 25) 1939. (i) Greene, C. H., and Hotz, R. Liver and Biliary Tract. A Review for 1938, *Arch. Int. Med.* **63** 778 (April) 1939. (j) Kapnick, I., Stewart, J. D., and Lyons, C. Plasma Prothrombin and Liver Function During Sulfonamide Therapy, *New England J. Med.* **227** 944 (Dec. 17) 1942. (k) Long, P. H., Haviland, J. W., Edwards, L. B., and Bliss, E. A. The Toxic Manifestations of Sulfanilamide and Its Derivatives with Reference to Their Importance in the Course of Therapy, *J. A. M. A.* **115** 364 (Aug. 3) 1940. (l) Ottenberg, R. Acute Yellow Atrophy of the Liver Following Sulfanilamide Therapy and Avertin Necrosis, *J. Mt. Sinai Hosp.* **6** 249 (Jan.-Feb.) 1940. (m) Price, A. E., and Myers, G. B. Treatment of Pneumococcal Pneumonia with Sulfanilamide, *J. A. M. A.* **112** 1021 (March 18) 1939. (n) Russell, H. K. Acute Toxic Necrosis of the Liver Following the Use of Sulfanilamide, *Ann. Int. Med.* **14** 168 (July) 1940. (o) Saphirstein, H. Hepatitis and Toxic Erythema with Desquamation Due to Sulfanilamide, *Urol. & Cutan. Rev.* **42** 101 (Feb.) 1938. (p) Spink, W. W. Sulfanilamide and Related Compounds in General Practice, ed. 2, Chicago, Year Book Publishers, Inc., 1942, p. 294. (q) Spring, M., and Bernstein, I. The Coexistence of Toxic Hepatitis, Acute Hemolytic Anemia and Renal Damage Following Sulfanilamide Therapy. Report of Two Cases, *Ann. Int. Med.* **14** 153 (July) 1940. (r) Tragerman, L. J., and Goto, J. M. Fatal Reactions to Administration of Sulfonamide Drugs, *J. Lab. & Clin. Med.* **25** 1163 (Aug.) 1940. (s) Watson, C. J. The Bile Pigments, *New England J. Med.* **227** 665 (Oct. 29), 705 (Nov. 5) 1942. (t) Watson, C. J., and Spink, W. W. Effect of Sulfanilamide and Sulfapyridine on Hemoglobin Metabolism and Hepatic Function, *Arch. Int. Med.* **65** 825 (April) 1940.

13 Bannick, Brown and Foster<sup>12a</sup> Fitzgibbon and Silver<sup>12f</sup> Garvin<sup>12g</sup> Gertler<sup>12h</sup> Ottenberg<sup>12i</sup> Saphirstein<sup>12o</sup>



some ended fatally<sup>14</sup> Toxic hepatic necrosis has also followed the use of the original prontosil (hydrochloride of 4'-sulfonamido-2'-4'-diaminoazobenzene) and azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate), either alone or in conjunction with sulfanilamide<sup>15</sup> Garvin<sup>12f</sup> observed an acute exfoliative dermatitis in 3 of his 5 cases of hepatitis resulting from sulfanilamide therapy, and Saphirstein<sup>12o</sup> reported a similar case

The most thorough studies of hepatic function in patients treated with sulfanilamide were carried out by Watson and Spink<sup>12t</sup> They demonstrated urobilinogenuria, elevated serum bilirubin or frank jaundice in an appreciable number of cases The jaundice was of the regurgitation type and was frequently associated with a direct van den Bergh reaction It was encountered chiefly when large therapeutic doses were employed, while after small doses, such as those frequently used in treating infections of the urinary tract, hepatic dysfunction was less apt to occur Similar findings were reported recently by Cantarow and Wirts<sup>12c</sup> Kapnick, Stewart and Lyons<sup>12j</sup> demonstrated a fall in plasma prothrombin as an early sign of hepatic dysfunction in the course of sulfonamide therapy De Bonis<sup>12e</sup> noted jaundice, enlargement of the liver and urobilinuria during the first week of sulfanilamide therapy in 2 cases Using tests for galactose tolerance and tests with aminoacetic acid, he found evidence of hepatic disturbance in 5 of 11 normal subjects after a dose of 0.003 Gm per kilogram of body weight Studies of hepatic function in cases of hemolytic anemia developing during sulfanilamide therapy have also revealed mild impairment in some instances<sup>16</sup>

Schmidt,<sup>17</sup> on the other hand, found no reduction in hepatic function, as judged by tests of galactose tolerance, during sulfanilamide therapy He was studying patients with gonococcal infections who were being treated with rather small doses He found that such patients often had reduced hepatic function before treatment and that sulfanilamide always had a favorable influence Sulfanilamide has also been used in isolated cases of obstructive jaundice and biliary cirrhosis associated with obstruction of the common bile duct<sup>18</sup> as well as in cases of suppurative pyelophlebitis and hepatic abscesses without evidence of aggravation of the antecedent damage to the liver<sup>19</sup>

Bannick, Brown and Foster<sup>12a</sup> observed 2 cases of jaundice following sulfanilamide therapy in which death occurred and in which there may have been pre-existing hepatic damage They felt that sulfanilamide may cause such preexisting damage to progress to a stage from which regeneration is impossible Watson<sup>20</sup> also has stated that in his experience severe and progressive hepatic injury is seen only when there is reason to believe that the liver was damaged before the admin-

14 Berger and Applebaum<sup>12b</sup> Cline<sup>12d</sup> Greene and Hotz<sup>12i</sup> Ottenberg<sup>12l</sup> Tragcrman and Goto<sup>12r</sup>

15 Gertler<sup>12h</sup> Russell<sup>12n</sup>

16 One patient studied by Ham and Deutsch (personal communication to the authors) had a severe hemolytic anemia from sulfanilamide, accompanied by severe damage to the liver with increased urobilinogenuria and diminished synthesis of hippuric acid The signs of hepatic insufficiency cleared promptly when administration of the drug was stopped See also Harvey and Janeway<sup>11</sup> and Watson and Spink<sup>12t</sup>

17 Schmidt, W. Leberfunktionsprüfungen bei Therapie mit Sulfamidkörpern, Klin Wchnschr **18** 953 (July 15) 1939, abstracted, J A M A **113** 1607 (Oct 21) 1939

18 Cleveland, W. H. Sulfanilamide Therapy in Presence of Severe Injury to the Liver and Jaundice, Proc Staff Meet, Mayo Clin **14** 680 (Oct 25) 1939

19 Ottenberg, R., and Berck, M. Sulfanilamide Therapy for Suppurative Pyelophlebitis and Liver Abscesses, J A M A **111** 1374 (Oct 8) 1938

20 Watson, C. J. The Effect of Sulfanilamide upon the Liver, Surger. **5** 616 (April) 1939, footnote 12s



istration of the sulfanilamide, for example, in the presence of severe infection or toxemia or when the drug was given to a patient who also received asphenamine treatment for syphilis. Among Kapnick's cases<sup>1-3</sup> the greatest reduction in plasma prothrombin occurred during treatment with sulfanilamide in a patient with known biliary cirrhosis who previously had a prolonged prothrombin time and had received vitamin K.

The implantation of sulfonamide compounds into the peritoneal cavity after abdominal operations is a procedure carried out with varying regularity by many surgeons, particularly when infection is present or anticipated. Because of its greater solubility, sulfanilamide is usually chosen for this purpose, and in a number of instances hepatic damage has resulted from its use in this manner.<sup>21</sup> In most of the cases oral doses were used in addition. While a considerable depression of hepatic function is thought by some surgeons to occur after any abdominal operation, regardless of the type of anesthesia used,<sup>22</sup> the damage to the liver in most of the patients treated with sulfonamide compounds could usually be attributed definitely to the drug and improved when treatment with it was discontinued. In some instances large doses (up to 20 Gm.<sup>1a</sup>) had been implanted. Possibly the high concentration attained, together with the sepsis, was responsible for the injury to the liver in certain cases. Blood from the portal vein may, for a short period after abdominal implantation of sulfanilamide, have a concentration of the drug 40 per cent higher than that in the peripheral venous blood<sup>1b</sup> but the levels are usually the same after about four hours.<sup>23</sup> Levels of 400 to 800 mg per hundred cubic centimeters of peritoneal fluid have been noted as long as forty hours after a single implantation of sulfanilamide.<sup>1</sup> Some surgeons have observed no serious local or general effects from the intraperitoneal use of this drug in many cases.<sup>25</sup>

Sulfapyridine, like sulfanilamide, has been found to produce damage to the liver both in experimental animals and in patients. In monkeys, sulfapyridine causes its greatest damage to the kidneys, but a "serious" hepatitis has been described.<sup>26</sup> Some of the hepatic cells appear vacuolated and contain large droplets, and pigment is seen in the Kupffer cells, but actual necrosis is not observed.<sup>27</sup> In rats, single or multiple doses of sodium sulfapyridine result in an elevation in blood sugar and an alteration in the storage and formation of glycogen which increases with the size of the dose.<sup>8</sup> No microscopic damage ascribable to sulfapyridine has been noted in experiments producing chronic toxicity in rats,<sup>28</sup> but foci of necrosis were

21 (a) Dees, J. G. A Valuable Adjunct in Perforated Appendices, *Mississippi Doctor* **18** 215 (Sept.) 1940. (b) Jackson, H. C., and Collier, F. A. The Use of Sulfanilamide in the Peritoneum. Experimental and Clinical Observations. *J. A. M. A.* **118** 194 (Jan. 17) 1942. (c) Ravdin, I. S., Rhoads, J. E., and Lockwood, J. S. The Use of Sulfanilamide in the Treatment of Peritonitis Associated with Appendicitis, *Ann. Surg.* **111** 53 (Jan.) 1940.

22 Boyce, F. F. The Role of the Liver in Surgery, *South Surgeon* **10** 56 (Jan.) 1941.

23 Pearce, A. E. Intraperitoneal Administration of Sulfanilamide, Correspondence. *J. A. M. A.* **120** 982 (Nov. 21) 1942.

24 Mueller, R. S., and Thompson, J. E. The Local Use of Sulfanilamide in the Treatment of Peritoneal Infections, *J. A. M. A.* **118** 189 (Jan. 17) 1942.

25 Thompson, J. E., Brabson, J. A., and Walker, J. M. The Intra-Abdominal Application of Sulfanilamide in Acute Appendicitis, *Surg., Gynec. & Obst.* **72** 722 (April) 1941. Mueller and Thompson.<sup>24</sup>

26 Antopol, W., and Robinson, H. Pathologic and Histologic Changes Following Administration of Sulfapyridine, with a Short Note on Sodium Sulfapyridine, *Arch. Path.* **29** 67 (Jan.) 1940.

27 Feinstein, W. H., and others. The Toxicity, Absorption and Chemotherapeutic Activity of 2-Sulfanilamidopyrimidine (Sulfadiazine), *Bull. Johns Hopkins Hosp.* **67** 427 (Dec.) 1940.

28 Walker, H. A., and van Dyke, H. B. Observations on the Toxicology of Sulfathiazole and Some Related Compounds, *J. Pharmacol. & Exper. Therap.* **71** 138 (Feb.) 1940.

noted in the livers of mice fed large doses of this drug<sup>29</sup> Like sulfanilamide, sulfapyridine seems to protect the livers of rats from damage by carbon tetrachloride<sup>30</sup> The failure of rats whose livers have been injured by phosphorus to show an increased glucuronate output while being given sulfapyridine and the resulting increase in urolithiasis<sup>31</sup> have already been mentioned

In human beings, fatty changes in the liver with fine globules uniformly distributed in the hepatic cells were noted by Brown, Thornton and Wilson<sup>30</sup> in all patients who died of pneumonia after sulfapyridine therapy This was interpreted as probably due to the toxicity resulting from the disease In 1 of their patients jaundice and enlargement of the liver developed, but eventually receded These workers later reported the findings of sulfapyridine in the liver from ten to forty days after the last dose,<sup>31</sup> but they would draw no conclusions as to whether sulfapyridine causes hepatitis Long and Wood<sup>32</sup> noted 1 patient with sulfapyridine-treated pneumonia who had hepatitis associated with jaundice in the absence of acute hemolytic anemia In the case reported by Cutts and Bowman<sup>33</sup> jaundice and aching in the right upper quadrant of the abdomen accompanied the hematuria and encephalopathy which followed the intravenous administration of 20 Gm of sodium sulfapyridine over a ten hour period All the symptoms subsided fairly promptly Two cases of hepatitis from sulfapyridine in children were reported by Leopold and Sobel<sup>34</sup> Spink<sup>12b</sup> and Watson and Spink<sup>12c</sup> encountered mild hepatitis in occasional sulfapyridine-treated patients, but they found much less disturbance of hepatic function than among the ones treated with sulfanilamide Others have also reported evidence of hepatic dysfunction, such as hyperbilirubinemia, urobilinogenuria<sup>35</sup> and decreased plasma prothrombin,<sup>12j</sup> in sulfapyridine-treated patients with pneumonia and other infections It should be mentioned, however that some patients with severe hepatitis have been successfully treated for pneumonia with sulfapyridine and have not shown any evidence of increase in the damage to the liver<sup>36</sup>

Sulfathiazole has proved less toxic to the liver than either sulfapyridine or sulfanilamide, both for laboratory animals and for human beings In dogs given large doses renal function is depressed but hepatic function is not affected<sup>37</sup> In

29 Rake, G, van Dyke, H B, and Corwin, W C Pathologic Changes Following Prolonged Administration of Sulfathiazole and Sulfapyridine, *Am J M Sc* **200** 353 (Sept) 1940

30 Brown, W H, Thornton, W B, and Wilson, J S Observations on the Absorption, Distribution and Excretion of Sulfapyridine, *J Clin Investigation* **18** 803 (Nov) 1939

31 Brown, W H, Thornton, W B, and Wilson, J S An Evaluation of the Clinical Toxicity of Sulfanilamide and Sulfapyridine, *J A M A* **114** 1605 (April 27) 1940

32 Long, P H, and Wood, W B, Jr Observations upon the Experimental and Clinical Use of Sulfapyridine II The Treatment of Pneumococcal Pneumonia with Sulfapyridine, *Ann Int Med* **13** 487 (Sept) 1939

33 Cutts, F B, and Bowman, R O Toxic Effects in Man of Overdosage with Sodium Sulfapyridine Report of a Case, *New England J Med* **225** 448 (Sept 18) 1941

34 Leopold, J S, and Sobel, I P Sulfapyridine Therapy in Pneumonias of Infancy and Childhood, *Arch Pediat* **56** 581 (Sept) 1939

35 Eif, L A, and McLeod, C M Increased Urobilinogen Excretion and Acute Hemolytic Anemia in Patients Treated with Sulfapyridine, *J Clin Investigation* **19** 451 (May) 1940 Cantarow and Wirts<sup>12c</sup>

36 Finland, M, Lowell, F C, and Strauss, E Treatment of Pneumococcal Pneumonia with Sulfapyridine, Sulfathiazole and Serum, *Ann Int Med* **14** 1184 (Jan) 1941 Brown, Thornton and Wilson<sup>31</sup>

37 Chmenko, D R, McChesney, E W, and Messer, F Continued Administration of Sulfathiazole on Renal and Hepatic Function in the Dog, *Proc Soc Exptl Biol & Med* **46** 124 (Jan) 1941

rats, sodium sulfathiazole produces a definite increase in blood sugar but does not affect hepatic glycogen unless highly toxic doses are used<sup>8</sup> Microscopic changes are seen in the livers of rats which receive large doses<sup>20</sup> No such lesions have been produced during the usual experiments for producing chronic toxicity in rats,<sup>28</sup> but they have been seen during similar studies on mice<sup>38</sup>

Isolated instances of hepatitis have been noted in patients receiving sulfathiazole in the usual therapeutic doses<sup>39</sup> In 1 patient hepatitis with severe jaundice and enlarged liver but without anemia accompanied the development of agranulocytosis This patient was treated for pneumonia and empyema by prolonged administration<sup>40</sup> of sulfathiazole Rammelkamp<sup>41</sup> observed a patient in whom, after a course of sulfathiazole therapy, fever, jaundice, and enlargement of the liver developed The complication cleared slowly when use of the drug was discontinued One month later the administration of a single dose of 0.5 Gm of the same drug was followed rapidly by a recurrence of the same symptoms Studies of hepatic function have shown some impairment during administration of sulfathiazole similar to that found in patients treated with sulfapyridine<sup>42</sup> Hepatic dysfunction, with bile and urobilinogen in the urine, decreased output of hippuric acid and retention of bromsulphalein, was noted in 1 case of hemolytic anemia following sulfathiazole therapy<sup>43</sup> In another case of acute hemolytic anemia from sulfathiazole, no hepatic dysfunction was demonstrated,<sup>44</sup> while in a third the liver was enlarged and tender<sup>45</sup> In a recent case<sup>46</sup> extensive focal necrosis of the liver, kidneys, spleen and adrenals was ascribed to the toxicity of sulfathiazole

Sulfamethylthiazole when given as the sodium salt to rats produces severe renal damage with nitrogen retention Associated with this there is also increased glycogen in the liver and definite hepatic injury<sup>17</sup> No gross or microscopic lesions attributable to this drug were noted during experiments for producing chronic toxicity in rats<sup>28</sup> There is little information concerning hepatic injury in human therapy, but sulfamethylthiazole drug has not been used extensively

Sulfadiazine produces no demonstrable damage to the liver in mice, rats or monkeys<sup>27</sup> Cantarow and Wirts<sup>12c</sup> found hepatic injury in 3 patients treated with sulfadiazine This was evidenced by bilirubinemia, urobilinogenuria, retention of bromsulphalein and diminished output of hippuric acid Kapnick, Stewart and Lyons<sup>12j</sup> observed a reduction of plasma prothrombin in 2 patients treated with sulfadiazine, but in 1 of them the prothrombin time returned to normal after five

38 Long, P. H. Thiazole Derivatives of Sulfanilamide Sulfathiazole and Sulfamethylthiazole, *J. A. M. A.* **114** 870 (March 9) 1940

39 Cantarow and Wirts<sup>12c</sup> Spink<sup>12p</sup> Finland, Lowell and Strauss<sup>30</sup>

40 McCarty, W. C., and Finland, M. Personal communication to the authors

41 Rammelkamp, C. H. Personal communication to the authors

42 Cantarow and Wirts<sup>12c</sup> Kapnick, Stewart and Lyons<sup>12j</sup>

43 Rothstein, I., and Cohn, S. Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy Case Report, *Ann. Int. Med.* **16** 152 (Jan) 1942

44 Quick, E. D., and Lord, F. D. Acute Hemolytic Anemia Following Sulfathiazole Administration Report of a Case with Recovery, *J. A. M. A.* **117** 1704 (Nov. 15) 1941

45 Bunin, J. J., and Israel, M. Acute Hemolytic Anemia Caused by Sulfathiazole, *Ann. Int. Med.* **16** 333 (Feb) 1942

46 Simon, M. A., and Kaufman, M. Death Following Sulfathiazole Therapy, *Canad. M. A. J.* **48** 23 (Jan) 1943

47 Lehr, D., Churg, S., and Antopol, W. Mechanism of Liver and Kidney Damage Caused by Sodium Sulfamethylthiazole, *Proc. Soc. Exper. Biol. & Med.* **45** 447 (Oct) 1940

days during which the patient continued to receive large doses of this drug. In our own<sup>48</sup> and in Spink's<sup>12p</sup> experience no evidence of damage to the liver has been noted in large numbers of sulfadiazine-treated patients with all types of infections. Some patients with severely impaired hepatic function have been treated with full doses of sulfadiazine for various diseases without ill effects and even with improvement in hepatic function during treatment.<sup>48</sup> Spink has recommended its use in cases of cirrhosis of the liver when a sulfonamide compound is indicated.<sup>12p</sup>

#### MATERIALS AND METHODS

The patients studied were all admitted to the Boston City Hospital during 1941 and the first half of 1942. Only those patients are included in whom there was clinical and laboratory evidence of damage to the liver and in whom tests of hepatic function were made before and after a course of some sulfonamide compound. In many of these cases repeated tests were made both during the sulfonamide therapy and for some time later. A large number of other similar patients treated with sulfonamide compounds were observed during this period, but they are not included here because of inadequate data.

In 13 of the cases a diagnosis of acute hepatitis was made, in them the damage to the liver was, for the most part, secondary to an acute pyogenic infection, except in 1 case in which a diagnosis of catarrhal jaundice was made. The remaining patients had chronic disease of the liver and included 14 with portal cirrhosis, 5 with biliary cirrhosis, 4 with damage to the liver resulting from chronic congestive cardiac failure and 1 with diffuse carcinomatosis.

To most of the patients the sulfonamide compound was given in the usual therapeutic doses and for a definite pyogenic infection. To a few, however, the drug was given because of a suspected infection, the presence of which was not substantiated. Sulfathiazole and sulfadiazine were each used alone for 14 patients, both were given in succession or on separate occasions to 7, and 2 received sulfapyridine. The average total dose per patient was 44 Gm. Those treated with both sulfathiazole and sulfadiazine received an average total dose of 56 Gm.

Several tests of hepatic function were employed and the icterus index was determined frequently in every case. The hippuric acid test was carried out according to the gravimetric method of Quick.<sup>1d</sup> A fractional bromsulphalein test was performed by injecting 2 mg of dye per kilogram of body weight and estimating the amount of dye retained after five and fifteen minutes, according to the method described recently by Deutsch.<sup>49</sup> The prothrombin time was measured by Souter and Kark's<sup>50</sup> modification of Quick's<sup>51</sup> method. Tests were made for bile in the urine, and its urobilinogen content was estimated by the dilution method of Wallace and Diamond<sup>52</sup> in most instances. In a few cases daily quantitative determinations of urobilinogen were made by the method of Watson.<sup>53</sup> Several of these tests were usually carried out in each case. The concentrations of sulfonamide compounds in the blood and the urine were determined at frequent intervals by the method of Bratton and Marshall.<sup>54</sup>

The clinical course of the patients was followed closely from day to day. Therapy for the disease of the liver included diets high in carbohydrate and protein and low in fat, brewers'

48 Finland, M., Strauss, E., and Peterson, O. L. Sulfadiazine: Therapeutic Evaluation and Toxic Effects in Four Hundred and Forty-Six Patients, *J. A. M. A.* **110** 2641 (June 14) 1941. Finland, M., Peterson, O. L., and Goodwin, R. A., Jr. Sulfadiazine: Further Clinical Studies of Its Efficacy and Toxic Effects in Four Hundred and Sixty Patients, *Ann. Int. Med.* **17** 920 (Dec.) 1942.

49 Deutsch, E. A Fractional Bromsulphalein Test to Determine Liver Damage in the Non-Jaundiced Patient, *New England J. Med.* **225** 171 (July 31) 1941.

50 Souter, A. W., and Kark, R. Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, *Am. J. M. Sc.* **200** 603 (Nov.) 1940.

51 Quick, A. J., Stanley-Brown, M., and Bancroft, F. W. A Study of the Coagulation Defect in Hemophilia and in Jaundice, *Am. J. M. Sc.* **190** 501 (Oct.) 1935.

52 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test for Liver Function, with a Description of a Simple Quantitative Method for Its Estimation, *Arch. Int. Med.* **35** 698 (June) 1925. This method may give false high readings during therapy with sulfonamide compounds.<sup>49</sup>

53 Watson, C. J. Studies of Urobilinogen. I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am. J. Clin. Path.* **6** 458 (Sept.) 1936.

54 Bratton, A. C., and Marshall, E. K., Jr. A New Coupling Component for Sulfanilamide Determination, *J. Biol. Chem.* **128** 537 (May) 1939.

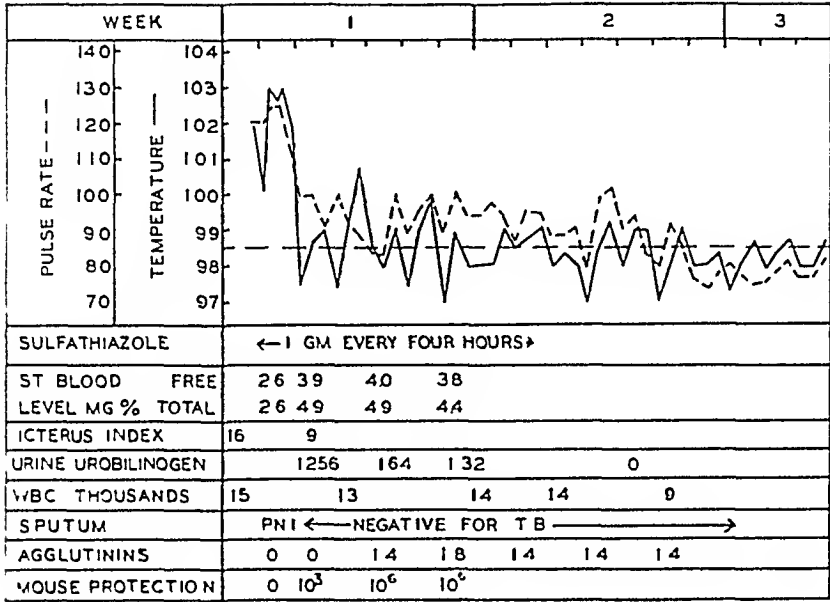


Chart 1—Clinical chart and relevant laboratory data in case 5. A man of 50 with type I pneumococcus lobar pneumonia involving the middle and the lower lobe of the right lung was admitted to the hospital on the sixth day of illness with mild jaundice, slightly enlarged liver and bile-stained urine. Blood culture showed no growth. The temperature and pulse rate dropped to normal after thirty-six hours of sulfathiazole therapy. The jaundice and the other symptoms of acute hepatitis improved rapidly thereafter.

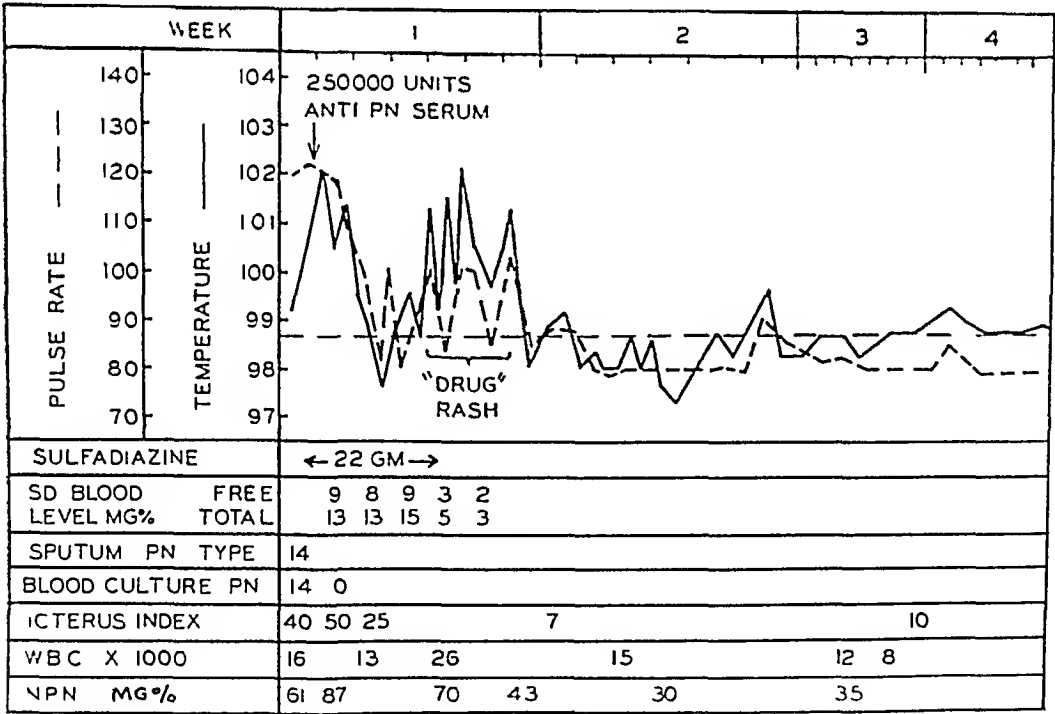


Chart 2—Chart of case 3. A man of 68 with a history of excessive intake of alcohol and a previous episode of jaundice thirty years ago was admitted to the hospital on the ninth day of a severe lobar pneumonia involving the upper lobe of the right lung. He had moderately intense jaundice of two days' duration. At entry the edge of the liver was felt 8 cm below the costal margin and was tender. After treatment with sulfadiazine and antipneumococcus serum the fever and toxic symptoms subsided, the jaundice cleared, and the liver edge receded gradually. The nonprotein nitrogen content of the blood was elevated at the time of the patient's admission to the hospital. It increased temporarily and then returned to normal after administration of the drug was stopped (see also table 1). This patient probably had underlying portal cirrhosis.

TABLE 1—Patients with Acute Hepatitis (? Toxic or Infectious Jaundice) Who Received Therapy with Sulfonamide Compounds

Results of Tests of Hepatic Function																				
Case, Sex and Age	Diagnosis	Before Therapy with Sulfonamide Compounds					After Therapy with Sulfonamide Compounds					Estimate of Hepatic Dysfunction	Therapy with Sulfonamide Compounds			Comments				
		Sulfonamide Compounds					Sulfonamide Compounds						Drug	Total Amount, Gm	Toxicity					
		I I	Bile in Urine	H A	Urine Urobilinogen	Prothrombin	I I	Bile in Urine	H A	Urine Urobilinogen	Prothrombin						B	S	P	
1 M 26	Pneumococcus, type 8 pneumonia	50	0	1 256	—	—	7	0	1 32	3 0	—	—	50	5	15	Mild	ST	41	Fever, rash	Rapid recovery
2 F 57	Pneumococcus, type 3 pneumonia	25	+	1 16	—	40	5	0	N	0 6	100	—	—	—	—	Severe	ST	33	NPN rise of 12 mg per 100 cc	Residual damage to liver at discharge
3 M 68	Pneumococcus type 14 pneumonia	50	+	1 32	1 3	56	10	0	N	1 0	80	30	5	—	—	Severe	SD	22	Fever, rash, NPN rise	Residual damage to liver (? cirrhosis) at discharge (chart 2)
4 F 30	Pneumococcus, type 3 pneumonia	80	0	1 64	3 4	—	10	0	N	2 5	100	—	—	—	—	Mild	SD	57	None	Complete recovery
5 M 50	Pneumococcus, type 1 pneumonia	16	+	1 256	—	—	9	0	N	—	—	—	—	—	—	Mild	ST	51	None	Complete recovery (chart 1)
6 F 55	Lobar pneumonia, parkinsonism	18	0	1 80	—	—	5	0	1 20	—	—	—	—	—	—	Mild	SD	17	None	Rapid recovery
7 F 42	B coli sepsis, ? liver abscesses chronic ulcerative colitis	60	+	1 128	0 7	100	6	0	N	3 0	100	—	—	—	—	Severe	ST SD	65 28	None	Gradual improvement of infection and hepatitis during chemo therapy
8 M 71	Carcinoma of colon postoperative sepsis in wound SA in plantation	110	+	15 mg *	1 8	40	10	0	7 mg *	2 2	55	30	0	—	—	Severe	ST	55	None	Hepatitis and sepsis improved under ST therapy
9 M 77	Pyelonephritis acute hepatitis	80	++	1 32	1 0	52	10	0	N	3 7	100	5	0	—	—	Mild	ST	10	None	Complete recovery, cause of hepatitis unknown
10 F 44	Acute hepatitis (? cause), streptococcal pharyngitis	90	—	1 256	1 5	63	10	0	N	2 7	—	—	—	—	—	Mild	SD	53	None	Rapid recovery
11 F 49	? Oltarrhal jaundice	75	++	1 256	1 5	100	10	0	N	3 0	—	5	0	—	—	Moderate	SD	26	None	Steady improvement on SD
12 F 28	Pyelonephritis, prostatic nancy, ulcerative colitis, peritonitis	75	+	—	—	—	25	++	—	0	—	—	—	—	—	Severe	ST SD	16 16	None	Died abscesses of liver found at autopsy, putrid empyema
13 M 71	Lobar pneumonia	75	++	—	—	—	10	0	—	—	—	—	—	—	—	Mild	SP	23	None	Cleared rapidly

Abbreviations I I, icterus index, urine urobilinogen, figures represent dilutions (method of Wallace and Diamond <sup>52</sup>); N, 1 16 or less (normal), H A, hippuric acid recovered from urine after ingestion of 6 Gm of sodium benzoate, prothrombin, concentration expressed in per cent of normal (Quick rapid method as modified by Soutter and Kark <sup>59</sup>), B S P, bromsulphalein, percentage retained in serum, SA, sulfanilamide, SP, sulfapyridine, ST, sulfathiazole, SD, sulfadiazine, NPN, blood nonprotein nitrogen in mg per 100 cc —, data not available

\* Watson method <sup>53</sup>, numbers represent milligrams per day

yeast or a preparation of autolyzed yeast (vegey) in doses of 6 to 12 Gm daily, parenterally administered vitamins and crude liver extracts when they seemed indicated and carbohydrate supplements in the form of corn syrup (Karo)

### RESULTS

*Patients with Acute Hepatitis*—The essential data concerning the 13 patients listed in this category are given in table 1. In 7 of the cases, the hepatitis was secondary to severe lobar pneumonia. In each of these 7 cases jaundice cleared and hepatic function improved with sulfonamide therapy. Chart 1 gives data for a typical case. Two of the 7 patients had evidence of some residual damage to the liver as indicated by diminished excretion of hippuric acid at the time of discharge from the hospital. One of these 2 patients (case 3, chart 2) had a high nonprotein nitrogen level in the blood at entry, and this increased appreciably during sulfadiazine treatment but returned to normal after the drug was stopped. The other patient (case 2) had a slight elevation of the level of nonprotein nitrogen in the blood during sulfathiazole treatment<sup>55</sup>. Both of these patients were clinically well when they left the hospital. The former probably had an underlying portal cirrhosis with acute hepatitis resulting from the pneumonia.

In 3 patients the cause of the acute hepatitis was uncertain. In 1 of them a diagnosis of catarrhal jaundice was made, and there was no evidence of any other infection. The second had a streptococcal pharyngitis and the third had a colon bacillus pyelonephritis. In each of these patients there was rapid recovery with steady improvement in hepatic function, which returned to normal during sulfathiazole or sulfadiazine therapy.

One of the patients (case 7), a woman of 60, had colon bacillus sepsis and probably multiple abscesses of the liver complicating chronic ulcerative colitis. She was treated first with sulfathiazole and then with sulfadiazine and showed gradual improvement both in the infection and in the hepatitis during the treatment. In another patient (case 12), a woman of 26, acute ulcerative colitis developed during the course of pregnancy, and she was admitted to the hospital because of rupture of the bowel, which was followed by peritonitis, generalized sepsis, acute hepatitis, pneumonia and putrid empyema. The jaundice improved during sulfathiazole and sulfadiazine therapy, but the patient died after two weeks. At autopsy multiple abscesses of the liver were found.

Case 8 is of special interest. In this patient, a man of 74, the peritoneal cavity was contaminated with feces in the course of a cecostomy performed to relieve a complete obstruction of the descending colon due to carcinoma. At the time of operation, 10 Gm of sulfanilamide was sprinkled into the peritoneal cavity and the cecostomy wound. On the following day there was evidence of both peritonitis and sepsis in the wound and the patient became jaundiced. Treatment with sulfathiazole was started, and a total of 55 Gm was given in nine days. During this time both the infection in the wound and the signs of peritonitis cleared, the icterus index dropped from 110 to 10, and the excretion of hippuric acid increased slightly. Two weeks later the bromsulphalein test showed no retention of the dye in fifteen minutes, but there was still an increased output of urobilinogen in the urine (7 mg per day by Watson method). An exploratory operation performed after five weeks revealed numerous metastases in the liver and omentum. The patient died four months later with progressive cachexia. This case presents a good example of acute hepatitis resulting from intraperitoneal sepsis and implantation of sulfanilamide, in which the hepatitis resolved when the infection was cured by administration of sulfathiazole.

<sup>55</sup> The excretion of hippuric acid is, of course, diminished in the presence of renal damage which is associated with retention of nitrogen.

*Patients with Chronic Disease of the Liver*—Twenty-four patients with chronic disease of the liver are included in this study. The damage to the liver was classified as severe in 13 of the cases and moderate in the remainder, except 1 in which it was considered to be mild. The clinical diagnosis was portal cirrhosis (Laennec) in 14 cases, biliary cirrhosis in 5 and chronic passive congestion or cardiac cirrhosis in 4, while in 1 case there was an old cirrhosis of undetermined type with superimposed metastatic carcinoma. The cases of portal cirrhosis occurred chiefly in patients with a history of prolonged and excessive alcoholic intake and faulty nutrition. The biliary cirrhosis was secondary to obstruction, resulting from stenosis of the common bile duct in 2 cases, from cholelithiasis in 2 others and from carcinoma of the gall-bladder in 1 case.

Sulfathiazole and sulfadiazine were each used alone in 9 cases, both were used either in succession or at different times in 5, while in 1 sulfapyridine was given. The drugs were used chiefly for the treatment of pneumonia, hemolytic streptococcal infections, such as pharyngitis or erysipelas, and infections of the urinary tract. They were given in full therapeutic doses.

All of the patients also received intensive therapy for their hepatic disease. The exacerbations and remissions which characterize the healing process in cirrhosis of the liver have frequently made very difficult an evaluation of the effects of the sulfonamide therapy. Furthermore, the oliguria so often associated with the severe relapses in the cases of portal cirrhosis would appear greatly to enhance the hazards of this form of treatment.

Some of the relevant data in these cases and the results of the tests of hepatic function carried out before and after the sulfonamide therapy are listed in table 2. So far as hepatic function is concerned, the patients with chronic disease of the liver seemed to tolerate the drugs well. Eleven of the patients showed improvement in hepatic function during sulfonamide therapy concomitant with the clearing up of the infection for which the drugs were given. In 11 other patients there was no apparent change in the status of the liver, although the infection in most of these cases was favorably influenced by the sulfonamide therapy. In 2 patients (cases 19 and 31) there may have been some temporary aggravation of the hepatic dysfunction during the chemotherapy at a time when they were manifesting other toxic reactions from the drugs.

In view of the role of the liver in the acetylation and detoxification of the sulfonamide compounds, it is of interest that the conjugation of these drugs in this group of patients was apparently unaffected. At least the percentage of drug found in the conjugated form (by the method of Bratton and Marshall<sup>54</sup>) both in blood and in urine of these patients was essentially the same as in the general run of patients without disease of the liver.<sup>56</sup>

A brief summary of 3 representative case reports will serve to indicate the variations in the results of the tests of hepatic function observed in some of the present cases.

CASE 25 (chart 3)—A 40 year old white laborer had been a heavy consumer of alcoholic beverages for fifteen years. For a year before he entered the hospital his appetite had been poor. His abdomen had been increasing in size for four or five months, and for the last five or six weeks he had noticed that his skin and scleras were jaundiced. At the time of admission

56 Peterson, O. L., Strauss, E., Taylor, F. H. L., and Finland, M. Absorption, Excretion and Distribution of Sulfadiazine (2-Sulfanilamido-Pyrimidine) *Am J M Sc* **201** 367 (March) 1941. Strauss, E., Lowell, J. C., Taylor, F. H. L., and Finland, M. Observations on the Absorption, Excretion, and Distribution of Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfamethylthiazole, *Ann Int Med* **14** 1360 (Feb) 1941.



TABLE 2—Relevant Data on Patients Treated with Sulfonamide Compounds Who Had Portal or Biliary Cirrhosis or Chronic Passive Congestion of the Liver (Cardiac Cirrhosis?)

Case, Sex and Age	Diagnosis	Results of Tests of Hepatic Function															Therapy with Sulfonamide Compounds	Comments (Effects of Therapy with Sulfonamide Compounds)			
		Before Therapy with Sulfonamide Compounds					After Therapy with Sulfonamide Compounds														
		I I	Bile in Urine	Pro throm bin	B S P			I I	Bile in Urine	Pro throm bin	B S P			of Hepatic Dysfunction	Drug	Total Amount, Gm			Toxicity		
14 M, 27	Pneumonia, Pn S portal cirrhosis	20	+	1 32	1 1	45	—	—	—	10	0	1 S	1 1	50	—	—	Severe	ST	40	Rash, fever	Improved while on ST
15 M, 48	Pneumonia Pn 14 portal cirrhosis	50	++	1 256	2 6	20	60	10	10	0	1 6	2 2	30	100	15	—	Severe	ST SD	35 33	Fever (ST)	Pneumonia improved, liver status unchanged
16 F, 46	Pneumonia, Pn 3 + SH, portal cirrhosis	35	+	1 128	2 5	100	—	—	10	0	N	0 5	—	—	—	—	Severe	ST SD	28 9	Fever (ST)	Infection increased damage to liver, Improved on ST
17 M, 57	Bronchopneumonia portal cirrhosis	<10	0	—	—	65	10	10	<10	0	—	0 7	—	—	10	20	Moderate	ST	72	NPN rose 20 mg per 100 cc	Pneumonia improved, liver status unchanged
18 M, 28	Bronchopneumonia, portal cirrhosis	35 10	++	1 128	3 1	68	70	5	5	0	1 1	—	100	—	—	—	Moderate	SD	25	Hematuria, renal colic	Liver status unchanged
19 M, 54	Bronchopneumonia portal cirrhosis	60 20	+	1 128	1 0	60	60	60	65 15	0	—	1 2	70	—	—	—	Moderate	SD†	36	Hematuria, colic, fever	Jaundice and ascites temporarily increased under SD
20 M, 55	Erysipelas, portal cirrhosis	100	—	1 256	1 6	35	—	—	8	—	1 32	—	80	—	—	—	Severe	SD	24	None	Good clinical response
21 M, 35	SH pharyngitis, portal cirrhosis	75	+	1 32	—	—	—	—	15	0	N	—	—	—	—	—	Moderate	SP	13	Hematuria, anuria 24 hrs	Rapid improvement with return of normal output of urine
22 F, 46	Pyelitis B coli, portal cirrhosis	25	+	1 32	0 8	39	90	15	6	0	1 8	1 8	100	—	—	—	Severe	ST SD	14 14	None	Steady improvement
23 M, 31	Portal cirrhosis	30	++	1 256 1 32	2 1 1 0	55	60	50	20	0	1 1	2 3	70	50	20	—	Moderate	ST	50	Rash, fever	Improved while on ST
24 M, 35	Portal cirrhosis	30 10	+	9 0 mg *	—	70	—	—	10	0	0 2 ml *	—	—	—	—	—	Moderate	SD	18	None	Died 4 months later of ruptured esophageal varix

25 M, 40	Portal cirrhosis	13	+	75* 13	1.8	65	100	10	10	0	0.97* 60 S	3.3	75	0	0	SD SD	75 17	None	Improved while on SD, (chart 3)
26 F, 41	Bronchopneumonia portal cirrhosis	110 60	0	0 2.2 mg*	2.1	90	—	—	12	0	0 1.8 mg*	2.0	—	60	20	SD	115	Agranulocytosis, fever	Liver status improved (chart 4)
27 M, 50	Pneumonia, SH, portal cirrhosis	7	0	1.128	—	60	70	50	10	0	1.128	2.1	85	10	20	Moderate SD	20 23	None	Liver status unchanged died 18 months later
28 F, 36	Postoperative pneumonia, biliary cirrhosis, c b d stenosis	100	++	1.6 mg*	1.2	50	—	—	100	++	2.6 mg*	1.0	100	—	—	Severe SD ST	20 19	None	No effect from SD, died of transfusion reaction
29 F, 43	Pneumonia, biliary cirrhosis, obstructive stenosis of c b d	60	++	0	0.8	60	—	—	50	++	1.128	1.5	90	—	—	Severe SD	30	None	Pneumonia improved, liver status unaltered (chart 5)
30 M, 50	Cholangitis biliary cirrhosis, cholelithiasis	150	++	0	0.8	100	—	—	100	++	0	0.4	80	—	—	Severe ST	64	None	Course unchanged
31 M, 52	Cholangitis, biliary cirrhosis cholelithiasis	30 75	++	1.8	1.2	98	—	—	65 85	++	1.4	2.9	—	30	20	Severe ST	30	Rash, fever	No effect, died 3 months later of ruptured varix
32 F, 63	Cholangitis, obstructive, biliary cirrhosis carcinoma of gallbladder, pneumonia, Pn 33	80	++	1.256	0.1	70	—	—	7	0	1.2	2.3	95	—	—	Mild SD	40	None	Improved by operation, died 3 months later of cancer
33 M, 58	Erysipeloid cirrhosis (? type), carcinoma of liver	<10	0	1.16	0.7	67	30	30	<10	0	1.16	—	80	—	—	Moderate ST	16	None	Infection improved died 10 days after ST stopped
34 M, 18	Active R H D with failure, O P O of liver	60	0	1.16	1.5	27	—	—	10	0	1.32	—	50	80	40	Severe ST	42	None	Died of R H D 1 month after ST stopped
35 M, 10	Pyelonephritis, Hyp H D, cardiac cirrhosis	10	0	1.32	—	100	70	5	8	0	1.4	—	80	60	50	Severe ST	60	None	Pyuria cleared, rest of course unaltered
36 F, 46	Pyelonephritis, B coli, cardiac cirrhosis	25	+	1.128	1.0	100	—	—	18	0	1.128	1.5	65	35	30	Moderate ST	18	None	Pyuria cleared rapidly, liver status unchanged
37 M, 26	Bronchopneumonia, R H D, O P O of liver	6	0	1.16	1.0	62	—	100	7	0	1.4	3.8	100	5	0	Moderate SD	18	None	General improvement on ST

Abbreviations (See table 1), Pn, pneumococcus, the number represents the type SH, streptococcus hemolyticus, R H D, rheumatic heart disease, O P C, chronic passive congestion, Hyp H D, hypertensive heart disease, c b d, common bile duct  
 \* Watson method, c numbers represent milligrams per day  
 † Given with equal amount of sodium bicarbonate

the patient was obviously jaundiced and numerous spider telangiectases were seen about the head, the shoulders and the upper parts of the arms. There were also two pulsating angiomas on the forehead. His abdomen was distended by ascites, and the hepatic dulness extended 10 cm below the costal margin. There was slight pitting edema of the legs and some hyperesthesia over the feet, and knee and ankle jerks were diminished. The significant laboratory data at that time (not shown in the figure) included the following values: icterus index, 25, plasma proteins, 5.2 Gm per hundred cubic centimeters, of which 2.3 Gm was albumin and 2.9 Gm globulin, prothrombin, 55 per cent of normal, and excretion of hippuric acid, 18 Gm (one week later it was only 0.34 Gm).

The patient was given a diet high in protein and carbohydrate and low in fat. This was supplemented by corn syrup and a preparation of autolyzed yeast, and the patient was also given large doses of liver extract intramuscularly. His urinary output was low during the first four weeks and then began to increase gradually. After five weeks he had improved somewhat and was given sulfadiazine in doses of 1 Gm every four hours for a week. The patient continued to improve while given the drug, and the ascites, which had remained stationary up to that time, began to clear with the onset of a pronounced spontaneous diuresis.

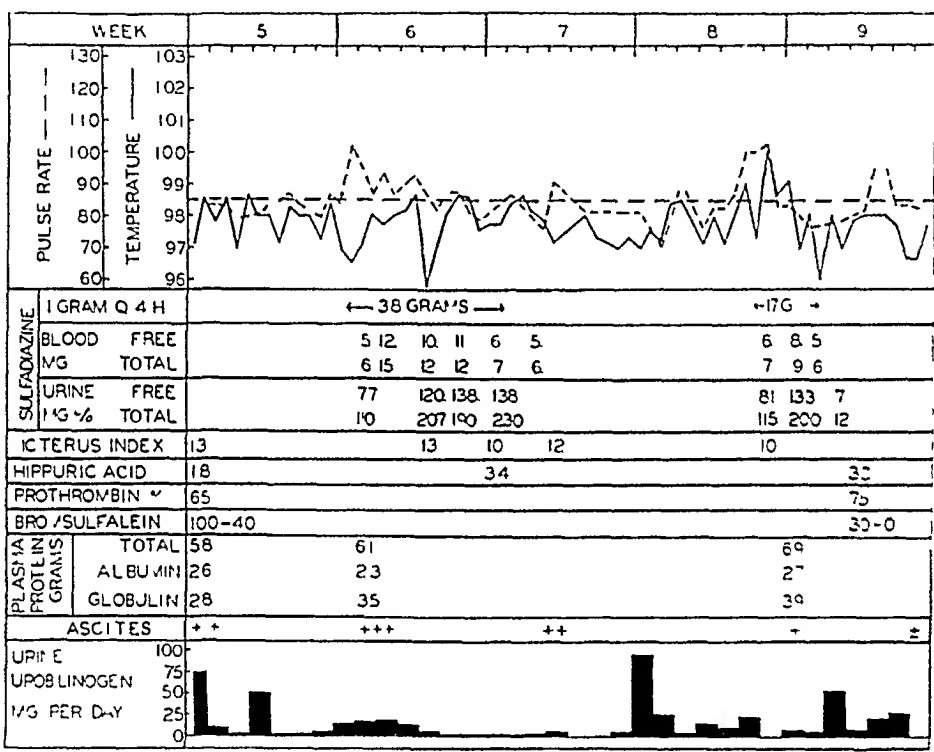


Chart 3—Clinical chart and laboratory data in case 25 for the fifth to the ninth week in the hospital. A summary of the case history is given in the text (see also table 2).

There was also an appreciable increase in excretion of urobilinogen in the urine, such as is often seen during improvement in hepatic function in patients with portal cirrhosis. Two weeks later the patient was given a second course of sulfadiazine for three days for a mild infection of the upper part of the respiratory tract, and equally favorable results were obtained.

The improvement in this patient's condition was probably a reflection of a spontaneous remission with regeneration and healing of the liver and is probably in no way related to the administration of sulfadiazine. It is significant, however, that the favorable course was in no way altered by the chemotherapy. Of interest also is the fact that only from 60 to 70 per cent of the drug recovered in the urine was determined as "free" sulfadiazine. This would suggest that there was an essentially normal conjugation (acetylation) of the drug in this patient.<sup>56</sup>

**CASE 26 (chart 4)**—A woman of 41 with a long history of alcoholism was admitted to the hospital after having symptoms of delirium tremens for three weeks. Nausea, vomiting, jaundice and dark urine had been present for five days. The patient was well nourished and moderately jaundiced. There were a few fine telangiectases over the forehead, the face and the neck. The edge of the liver was felt 4 cm below the costal margin, and a small amount of ascites was made out. She was considered to have portal cirrhosis and was given

a diet high in protein and carbohydrate and low in fat. This was supplemented with yeast and parenteral injections of liver extract. During the patient's second week in the hospital, because of persistent fever and signs of bronchopneumonia, the administration of 1 Gm of sulfadiazine every four hours was begun. The jaundice was subsiding at the time, and the icterus index had dropped from 110 to 40. Use of the drug was inadvertently continued for

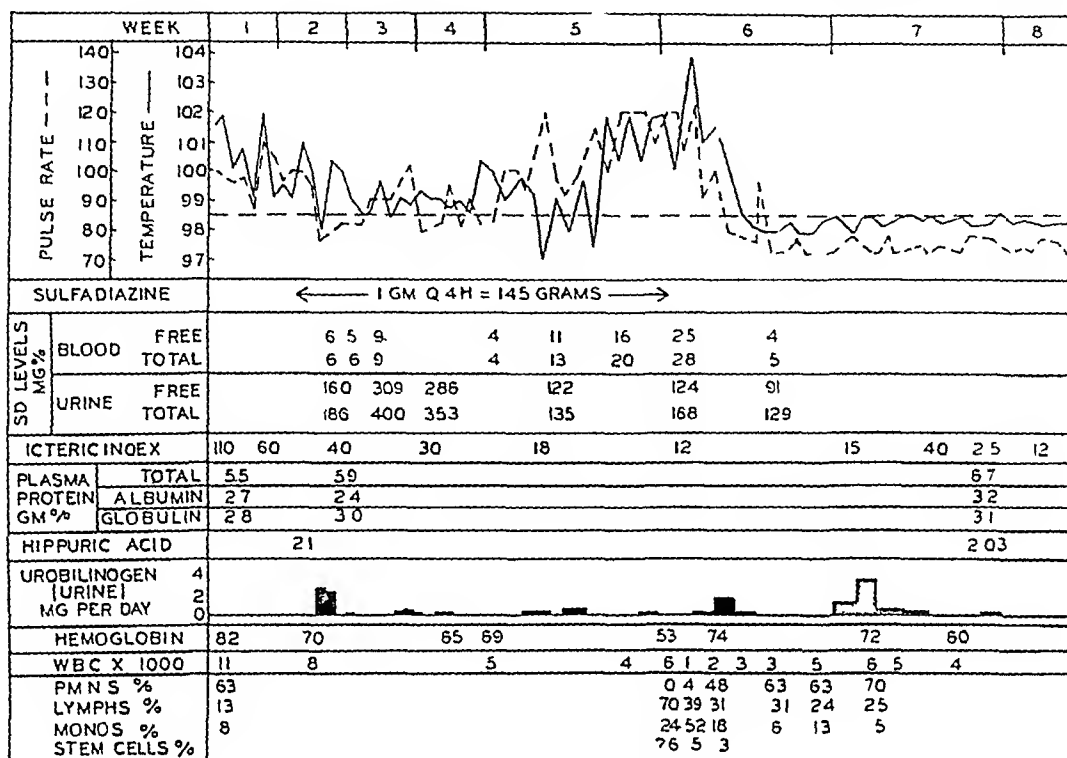


Chart 4—Clinical chart and laboratory data in case 26. This case has been reported by Curry,<sup>57</sup> and a brief summary of the clinical observations is given in the text.

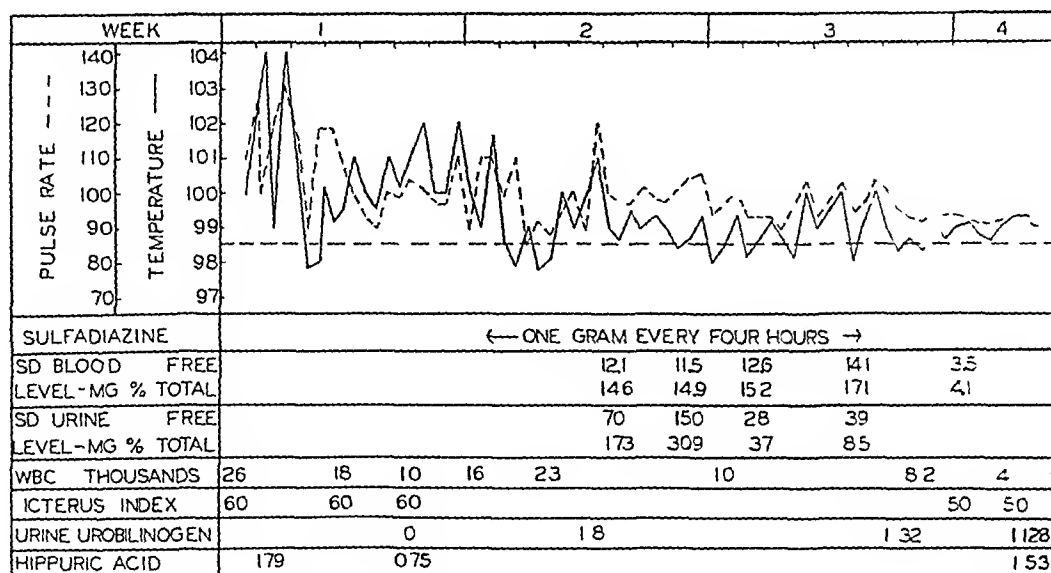


Chart 5—Relevant data in case 29, a brief summary of which is given in the text.

twenty-four days, at the end of which time fever and agranulocytosis developed. Chemotherapy was then stopped, and the leukocyte count returned to normal in a few days. During the administration of sulfadiazine the hepatic function did not seem to be affected adversely and, in fact, continued to improve. There was a recurrence of the jaundice and a transient rise in the icterus index to 40 during the second week after use of the drug was stopped and

well after the temperature and leukocyte count had returned to normal This case has been reported in greater detail by Dr Curry<sup>57</sup>

CASE 29—A woman of 43 was admitted to the hospital because of fever, cough and bile-stained purulent sputum of several days' duration She had had a cholecystectomy fourteen years previously and had become jaundiced one month after the operation The jaundice had persisted in varying degrees ever since and was not improved after a laparotomy which was performed nine years later At the time of entry she was moderately jaundiced, the liver edge was felt 7 cm below the costal margin and the edge of the spleen was also palpable The icterus index was 60, and the prothrombin level was 60 per cent of normal The excretion of hippuric acid was 1.79 Gm at that time and 0.75 Gm one week later Because of persistence of fever, leukocytosis and signs of pulmonary consolidation, the patient was given sulfadiazine in doses of 1 Gm every four hours The pneumonia improved promptly, but there was essentially no change in the jaundice and in the results of tests of hepatic function during or after the therapy (table 2 and chart 5)

*Toxicity of Sulfonamide Compounds*—The important and severe toxic effects of sulfonamide therapy encountered in this series of cases are summarized in table 3 according to both the underlying hepatic disease and the drug used

TABLE 3—Toxic Manifestations from Sulfonamide Compounds in Thirty-Seven Patients with Disease of the Liver

Toxic Effect	Acute Hepatitis (11 Cases)	Portal Cirrhosis (14 Cases)	Biliary Cirrhosis (5 Cases)	Chronic Passive Congestion and Miscellaneous (5 Cases)	ST (21 Cases)	SD (21 Cases)	SP (2 Cases)	Total (37 Cases)
Fever alone	0	2	0	0	2†	0	0	2
Rash and fever	2	2	1	0	4	1	0	5
Urinary tract (hematuria, colic anuria, etc)	0	3†	0	0	0	2	1	3
Nitrogen retention *	1	1	0	0	2	0	0	2
Agranulocytosis	0	1†	0	0	0	1	0	1
Total	3	9	1	0	8	4	1	13
Percentage of cases	23	61	20	0	38	19	50	35

For abbreviations see tables 1 and 2  
\* Without hematuria, etc  
† One patient also had fever  
‡ 7 patients received both ST and SD, 2 of these had fever from ST and not from SD

They are noted for the individual cases in tables 1 and 2 It is apparent that the serious complications were particularly frequent among the patients with portal cirrhosis Renal complications, including retention of nitrogen, occurred in 4 patients This high incidence is ascribable, in part, to the low urinary output of these patients, most of whom had edema and retention of water which responded rather poorly to treatment with diuretic drugs In most of the other patients with portal cirrhosis, however, there was no evidence of renal irritation, although the daily output of urine ranged only between 500 and 1,200 cc Administration of alkali in the form of sodium bicarbonate to these patients resulted in further retention of water and was therefore not as useful in preventing renal complications as it appears to be for patients who have a normal water metabolism<sup>58</sup> In the remaining patients with chronic damage to the liver and in those with acute hepatitis, all the toxic effects of the sulfonamide compounds were less frequent than in the patients with portal cirrhosis, but the numbers of

57 Curry, J J Acute Agranulocytosis Following Sulfadiazine, J A M A 119 1502 (Aug 29) 1942  
58 Peterson, O L, Goodwin, R A, Jr, and Finland, M Observations on the Urinary Excretion of Sulfadiazine, J Clin Investigation 22 659 (Sept) 1943

patients are too small to permit one to judge whether or not such effects were more frequent than in patients without damage to the liver.

Sulfathiazole and sulfadiazine were each used for 21 patients, including 7 who received both drugs either in succession or at different times. Toxic manifestations of the type listed in table 3 were twice as frequent during administration of sulfathiazole as they were during sulfadiazine therapy. Essentially the same relative frequency of toxic reactions has been noted from these two drugs in patients without disease of the liver. Of the 7 patients who received both drugs, 2 had fever from sulfathiazole only.

#### COMMENT

Although the number of cases studied is small, the results presented seem to be fairly consistent and warrant certain conclusions. The excellent results obtained after the administration of sulfathiazole and sulfadiazine (and probably also of sulfapyridine) to patients with acute hepatitis were striking. The successful treatment of the underlying infectious process produced rapid recovery from the damage to the liver. All the patients showed complete clinical recovery before they left the hospital, although 2 of them still showed evidence of residual damage, as indicated by tests of hepatic function. Acute hepatitis secondary to a bacterial infection calls for energetic treatment with full doses of such effective sulfonamide compounds as sulfathiazole and sulfadiazine instead of contraindicating their use. Complications of such chemotherapy appear to be no more frequent in this group than in patients with normal hepatic function.

In patients with chronic disease of the liver the results were not so striking. It is significant, however, that most of these patients had severe damage to the liver, and yet sulfathiazole or sulfadiazine did not aggravate their hepatic disease enough to produce measurable changes in the results of the functional tests that were employed. In the 2 patients who appear to have been made worse by the drugs, either the changes noted were coincident with the natural fluctuations in the disease or they were in some way related to the toxic manifestations of the drug. It is fair to conclude, however, that in cases of chronic damage to the liver, as in cases of acute hepatitis, sulfathiazole or sulfadiazine need not be withheld when their use is otherwise indicated. Some additional caution seems warranted in their use for chronic disease, particularly in order to insure an adequate urinary output.

In the patients with portal cirrhosis there are often associated diseases such as alcoholism, faulty nutrition or specific vitamin deficiencies and water retention. The possibility of interference with the utilization of vitamins, such as nicotinic acid and thiamine, by drugs like sulfapyridine, sulfathiazole and sulfadiazine because of certain chemical similarities, warrants some consideration.<sup>59</sup> It is doubtful, however, whether this factor is of any clinical significance, even in cases like the ones under discussion here.

The high incidence of toxic reactions to the sulfonamide therapy in patients with portal cirrhosis lends further weight to the contention that the liver is concerned in the "detoxification" of sulfonamide compounds. This process is probably different from the usual "conjugation" or "acetylation," such as one measures in determining the "free" and "total" sulfonamide compounds by the method of Bratton and Marshall.<sup>54</sup> The values obtained in blood and in urine by this method indicate relatively normal conjugation. The high incidence of renal complications, however, suggests the possibility that there is a failure to form soluble conjugates, such as glucuronates or ethereal sulfates, as noted by Scudl and his associates.<sup>3</sup>

<sup>59</sup> Janeway, C. The Sulfonamides. I. Their Mode of Action and Pharmacology, New England J. Med. **227** 989 (Dec 24) 1942.

The frequency of other toxic manifestations, such as drug fevers, rashes and agranulocytosis, may also depend on the failure of some as yet unexplained form of detoxification by the liver

Patients with hepatic dysfunction secondary to cardiac failure seemed to tolerate sulfathiazole and sulfadiazine about as well as those with acute hepatitis. The degree of hepatic dysfunction appeared to depend on the course of the underlying disease and apparently was unaffected by the chemotherapy. It has been pointed out previously that in cases of congestive cardiac failure complicated by bacterial infections, particularly if the respiratory tract is involved, the sulfonamide compounds may be extremely helpful.<sup>60</sup> With improvement of the infection, the cardiac decompensation responds more readily to rest and to digitalis therapy. Under these conditions, the accompanying diuresis often decreases the possibilities for renal complications.

It should be pointed out in closing that the possibility of damage to the liver by any of the sulfonamide compounds used in this series of cases has not been excluded by the observations presented. Such damage may occur under unusual conditions, for example, in patients with specific sensitiveness or idiosyncrasies, and when considerable retention of the drug occurs because of renal insufficiency or because excessive and toxic doses are employed either accidentally or for special purposes.

#### SUMMARY AND CONCLUSIONS

The effects of the administration of sulfonamide compounds, particularly sulfathiazole and sulfadiazine, on the clinical course and hepatic function have been studied for 37 patients with various types of damage to the liver.

In the patients with acute hepatitis associated with bacterial infections, the sulfonamide therapy was almost invariably associated with improvement in hepatic function which paralleled the improvement in the underlying infection.

In the patients with chronic damage to the liver hepatic dysfunction was not aggravated by administration of sulfathiazole or sulfadiazine. There was some improvement noted as a result of such therapy in cases in which bacterial infection was adding to the hepatic injury.

Severe toxic effects of sulfonamide therapy other than direct injury to the liver were unusually frequent in the patients with portal cirrhosis and were twice as common after sulfathiazole as after sulfadiazine.

It is concluded that the presence of damage to the liver should not be considered a contraindication to therapy with sulfathiazole or sulfadiazine in patients with bacterial infections against which these drugs are effective. Sulfadiazine is the drug of choice in such cases. Caution should be exercised in the administration of sulfonamide compounds to patients with severe portal (Laennec's) cirrhosis of the liver.

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<sup>60</sup> Finland, M., Peterson, O. L. and Strauss, E. Some Uses and Abuses of Chemotherapy in Pneumonia, *New England J. Med.* **225**: 601 (Oct 16) 1941.

# RHYTHMIC PROPERTY OF THE HUMAN HEART

MORRIS H NATHANSON, M D

LOS ANGELES

The heart is a contractile organ, but it possesses important properties aside from that of contractility. The functions of rhythmicity, conductivity and irritability are also of fundamental importance in cardiac physiology. The clinician's attention is focused mainly on the contractile function of the heart, since the usual methods of examination, palpation of the apical impulse, auscultation of cardiac sounds and inspection of the heart by the fluoroscope, are means by which this property of the heart may be investigated. Furthermore, impairment of contractile efficiency is the basis for the most frequent manifestation of heart disease, congestive heart failure.

Rhythmicity is the property of stimulus formation, and since the heart is an automatic organ producing its own stimulus, it is obvious that this function is essential in the normal physiologic processes of the heart. If the rhythmic function is so reduced that no stimulus is produced, there is a sudden cessation of activity in a heart which may be entirely competent in its contractile power. This is the situation in the cardiac type of syncope associated with a hyperactive carotid sinus and in the ventricular standstill of heart block. On the other hand, there may be an increase in rhythmicity of certain portions of the heart. This leads to the development of ectopic rhythms and is related to the most serious cardiac arrhythmia, ventricular fibrillation. The mechanism of ventricular fibrillation is not definitely established, but there is evidence that the development of ectopic ventricular foci of rhythmicity plays an important part in the genesis of this arrhythmia. Wiggers<sup>1</sup> has demonstrated that an ectopic ventricular beat developing during a vulnerable phase in the heart cycle will consistently result in ventricular fibrillation. Ventricular fibrillation, either occurring spontaneously or induced experimentally, is preceded usually by a period of ectopic ventricular rhythm. Various drugs which increase ventricular rhythmicity, such as epinephrine or barium chloride, will induce ventricular fibrillation when administered in toxic doses or when given with other drugs. It has been demonstrated that ventricular fibrillation is the result of the synergistic action of epinephrine, a drug which increases ventricular rhythmicity, and a variety of substances, including chloroform<sup>2</sup>, barium chloride,<sup>3</sup> benzene<sup>4</sup> and cyclopropane<sup>5</sup>.

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From the University of Southern California School of Medicine

1 Wiggers, C J. The Mechanism and Nature of Ventricular Fibrillation, *Am Heart J* **20** 399, 1940

2 Levy, A J, and Lewis, T. Heart Irregularities Resulting from the Inhalation of Low Percentages of Chloroform Vapour, and Their Relationship to Ventricular Fibrillation, *Heart* **3** 99, 1912

3 Rothberger, C J, and Winterberg, H. Ueber die experimentelle Erzeugung extrasystolischer ventrikularer Tachycardia durch Accelleranreizung, *Arch f d ges Physiol* **142** 461, 1911

4 Nahum, L H, and Hoff, H E. The Experimental Production of Ventricular Fibrillation and Its Prevention by  $\beta$  Methyl Acetyl Choline Chloride, *Am J Physiol* **109** 78, 1934

5 Oith, O S, Leigh, M D, Mellish, C H, and Stutzman, J W. Action of Sympathomimetic Amines in Cyclopropane, Ether and Chloroform Anaesthesia, *J Pharmacol & Exper Therap* **67** 1, 1939



It is clear that while a disturbance in contractile efficiency is the basis for the comparatively slowly developing congestive failure, sudden cessation of cardiac activity is a result of a disturbance in the rhythmic property of the heart<sup>6</sup>. Thus, a depression of cardiac rhythmicity leads to cardiac or ventricular standstill (hyperactive carotid sinus or heart block), while increased ventricular rhythmicity predisposes to ventricular fibrillation, which is generally accepted as the usual mechanism of sudden death due to a cardiac condition. It is therefore evident that the rhythmic property of the heart is of interest not only to the physiologist but to the clinician, so that he may have an intelligent approach to the therapy of disturbances of this function of the myocardium.

The exact nature of the heart's internal stimulus is unknown, and information concerning the factors influencing the rhythmic function is still incomplete. There are a number of theories suggesting a rhythmic development of a chemical or a physical state in the myocardium as the underlying process. The stimulus is developed in that part of the heart which is capable of producing these changes most rapidly. Ordinarily, this takes place in the sinus node. Other portions of the specialized tissue can produce the stimulus but are held in abeyance by the greater activity of the sinus node. A variety of factors can influence the rhythmic function, including temperature, hydrogen ion concentration and the presence or absence of certain inorganic salts. Particularly as with other properties of the heart, the rhythmic function is influenced by the cardiac innervation, the parasympathetic nerves having a depressing action and the sympathetic nerves a stimulating effect.

The present report deals with observations on the rhythmic function of the human heart as influenced by modification of the cardiac innervation. The cardiac innervation was affected in the following manner: (1) parasympathetic stimulation mechanically by pressure on the carotid sinus and chemically by the use of mechoyl chloride (acetylbetamethylcholine chloride) and (2) sympathetic stimulation by the use of epinephrine and related compounds. In this report data regarding several phases of the subject are included. These consist of (1) the influence of age and sex and the presence of heart disease on cardiac inhibition by stimulation of the vagus nerve, (2) the efficiency of ectopic rhythmic centers of the human heart, (3) the distribution of the cardiac innervation to the rhythmic foci of the heart, (4) the action of drugs on reflex vagal inhibition of the heart and (5) the influence of drugs on depressed and on increased rhythmicity of the human heart.

#### INFLUENCE OF AGE, SEX AND DISEASE ON VAGAL INHIBITION OF THE HEART

In carrying out observations on the effect of pressure on the carotid sinus in a large group of subjects over a period of years it was found that the cardiac response was influenced by several factors, including age, sex and presence or absence of cardiac disease.

*Age*—Pressure over the carotid sinus usually depresses the heart rate slightly or not at all in persons below the age of 40. Between 40 and 50 there is an increase in the number of persons responding and in the intensity of the response. However, most of the hyperactive reactions in which a cardiac standstill was induced were obtained in subjects above the age of 50. In a previous report<sup>7</sup>

6 Nathanson, M. H. Pathology and Pharmacology of Cardiac Syncope and Sudden Death, *Arch. Int. Med.* **58** 685 (Oct.) 1936.

7 Nathanson, M. H. Site of the Exaggerated Sinus Caroticus Reflex, *Proc. Soc. Exper. Biol. & Med.* **29** 1037, 1932.

it was demonstrated that this increased response with increased age was not due to sclerosis of the carotid artery in the region of the carotid sinus but that it actually represented an increased reactivity of the vagus nerve. This confirms other observations indicating that vagal action increases with age. A more intense vagal effect has been noted in old cats as compared with young kittens.<sup>8</sup> In human beings after paralysis of the vagus nerve endings with atropine there is an increase in the degree of pulse acceleration up to the age of 30 and then a decrease, so that in old age there is little or no acceleration.<sup>9</sup> Gilbert<sup>10</sup> in human subjects also demonstrated an increased cardiac response to stimulation of the vagus nerve with increase in age, as did Sigler<sup>11</sup> in his studies.

*Sex*—The response of the heart to pressure on the carotid sinus is much more marked in the male than in the female. In the female only a moderate slowing of the heart rate can be obtained even at advanced ages. In a period of five years, during which a prolonged cardiac standstill was noted in more than 100 male patients, this hyperactive reaction was noted in only 6 females. These observations indicate that in conditions, such as attacks of tachycardia of supraventricular origin, in which stimulation of the vagus nerve is desirable, an effect will more likely be obtained in a person of advanced years and of the male sex.

*Presence of Cardiac Disease*—Before the discovery of the carotid sinus reflex many studies were carried out on the effect on the cardiac mechanism of pressure over the sheath of the carotid artery. This procedure was interpreted as a direct stimulation of the vagus nerve, and the studies were called "vagus pressure studies." There is some difference of opinion as to the significance of the various types of response, but there are several reports in the literature suggesting that a hyperactive cardioinhibitory response to pressure over the carotid sinus is frequently associated with coronary disease.<sup>12</sup> Braun and Samet<sup>13</sup> showed that the effect of stimulation of the vagus nerve was markedly increased in cats when branches of the left coronary artery system particularly were ligated. They concluded that damage to ventricular musculature increases the irritability of the vagus nerve. More recently, Sigler<sup>14</sup> concluded that coronary disease is the condition in which the reflex occurs with the greatest frequency and the highest degree of response. Early in my experience the great frequency of a hyperactive response in persons with coronary disease was noted. Of the first 40 subjects in whom a cardiac standstill was induced by pressure over the carotid sinus, there was evidence of coronary disease of the anginal type in 34. Of patients having coronary disease with angina, a hyperactive response was obtained in about one third. In the remaining two thirds the response was no more intense than may be obtained in normal subjects of the same ages. In young subjects and in females in whom a hyperactive response was obtained the incidence of coronary

8 Albutt, T. C. *Diseases of the Arteries and Angina Pectoris*, London, Macmillan & Co., 1915.

9 Cushny, A. R. *Textbook of Pharmacology and Therapeutics*, Philadelphia, Lea & Febiger, 1918.

10 Gilbert, N. C. The Increase of Certain Vagal Effects with Increased Age, *Arch. Int. Med.* **31** 423 (March) 1923.

11 Sigler, L. H. Clinical Observations on the Carotid Sinus Reflex, *Am. J. M. Sc.* **186** 118, 1933.

12 Wenckebach, K. F., and Winterberg, H. *Die unregelmässige Herzthätigkeit*, Leipzig, Wilhelm Engelmann, 1927, p. 128.

13 Braun, L., and Samet, B. Vagusdruck und Koronargefäss, *Deutsches Arch. f. klin. Med.* **161** 257, 1928.

14 Sigler, L. H. Hyperactive Cardioinhibitory Carotid Sinus Reflex, *Arch. Int. Med.* **67** 177 (Jan) 1941.

disease was especially high. Siglei<sup>14</sup> stated that the more severe the coronary disease, the more apt the reflex is to occur and the greater is its degree. In my experience there did not appear to be any correlation between the severity of the disease and the presence or intensity of the reflex. A hyperactive response was frequently noted in instances of milder disease and a negative reaction observed in cases of more severe disease. However, I agree with Siglei that a hyperactive reaction may be an aid in making a diagnosis of coronary disease in persons with suggestive signs and symptoms.

#### EFFICIENCY OF ECTOPIC RHYTHMIC CENTERS

It is well known that after the normal rhythmic center of the heart, the sinus node, is temporarily or permanently eliminated, the heart will continue to beat, since new rhythmic centers become active. Eyster and Meek<sup>15</sup> have shown that extirpation of the sinus node is followed by a rhythm arising either in the main portion of the auriculoventricular node or in an extension of this node around the mouth of the coronary vein. Cohn, Kessel and Mason<sup>16</sup> after removing the sinus node in dogs, observed a transitory standstill of the heart, the duration varying from four seconds to three minutes, the interval being less than thirty seconds in most instances. The period of standstill represents the time required for some other portion of the heart to assume the pacemaking function. This variation in the time necessary for ectopic centers to function indicates a considerable variation in the rhythmic efficiency of ectopic centers in different animals. This type of experiment can be performed on many human subjects, since it is possible to eliminate the sinus node for relatively long periods by pressure on the carotid sinus.

In a series of electrocardiographic studies on elderly male subjects during application of pressure over the carotid sinus a hyperactive response was obtained in 34 subjects. After pressure over the carotid sinus the heart was deprived of its normal pacemaker for intervals varying from five to fifteen seconds. In 6 instances the elimination of the normal pacemaker was followed promptly by an ectopic rhythm of ventricular origin (fig 1 *A*), so that a cardiac arrest did not occur. In 25 subjects a prolonged cardiac standstill was induced, as there was no spontaneous tendency for ectopic centers to become active during the period of inactivity of the sinus node (fig 1 *B* and *C*). In most instances repeated performance of the experiment yielded a consistent response. In 3 subjects the reaction was variable, resulting in a cardiac standstill on one occasion and in a ventricular rhythm on repetition of the experiment. These observations indicate that there is a variation in different subjects in the rhythmic activity of ectopic centers and in most persons a relatively low efficiency of secondary rhythmic centers in the heart. This, undoubtedly, accounts for the variable reaction which follows a transition from normal rhythm to heart block. In those persons in whom the Adams-Stokes syndrome (ventricular stoppage) appears the rhythmic efficiency of the ventricular centers is low and a ventricular arrest precedes the development of rhythmic activity of the ventricular centers. In those persons in whom there is no ventricular standstill the rhythmic efficiency of the ventricular centers is such that they become active almost immediately after the ventricles are deprived of the stimulus from the auricles.

15 Eyster, J. A. E., and Meek, W. J. Studies on the Origin and Conduction of the Cardiac Impulse, *Am J Physiol* **61** 117, 1922.

16 Cohn, A. E., Kessel, L., and Mason, H. H. Observations on the Function of the Sino-Auricular Node in the Dog, *Heart* **2** 311, 1912.

DISTRIBUTION OF THE CARDIAC INNERVATION TO RHYTHMIC  
FOCI OF THE HEART

The influence of the vagus and the sympathetic nerves is not exerted equally on different portions of the heart. The sinus node is predominantly under the influence of the vagus nerve, although sympathetic fibers supply the node. Increases in heart rate due to exercise or to emotional excitement are a result primarily of lessening of vagal tone, rather than of an increase in sympathetic activity. The statement is generally made that the vagus nerves exert their influence predominantly on the auricles, while the sympathetic nerves exert their effect mainly on the ventricles. Physiologic studies on experimental animals indicate a variation in different species and in different animals of the same species. This variation in response has to do chiefly with the effect of the vagus nerve on the ventricles, and the reports are not entirely in agreement. Lewis<sup>17</sup> stated that in dogs in which the auriculoventricular bundle has been destroyed "a vagal influence on the ventricle is neither powerful nor invariable, while the sympathetics seem to possess a definite influence." Puddu,<sup>18</sup> however, concluded that the ventricular rate of dogs having complete heart block could be slowed by stimulation of the

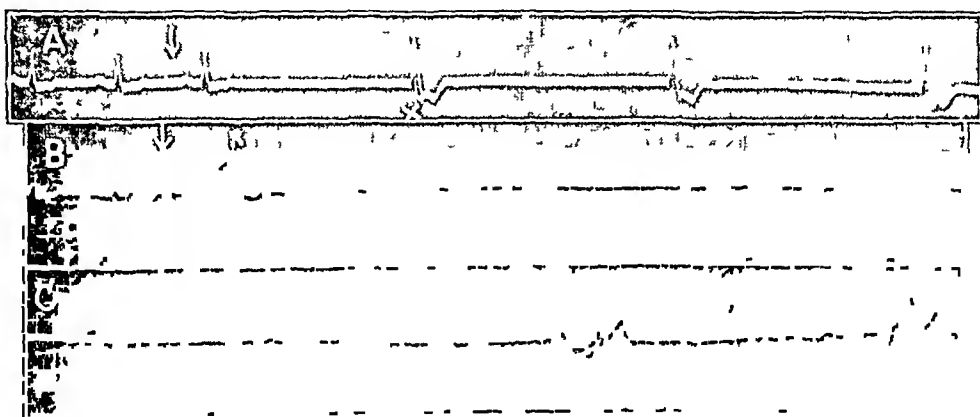


Fig 1—A, pressure on the carotid sinus (arrow) eliminates the sinus node, and a slow rhythm arising from an ectopic ventricular focus appears at X. B and C form a continuous strip showing a standstill of fifteen seconds induced by pressure on the carotid sinus. There is no tendency for ectopic rhythmic foci to become active. Cardiac activity is resumed only when the sinus node again functions.

vagus nerve. Lewis<sup>17</sup> also stated that while the vagus nerve has an influence on the fibrillating auricle, there is no effect on the fibrillating ventricle. Garrey and Bass<sup>19</sup> concluded that the ventricle of the frog is supplied with fibers from the vagus nerve, while that of the turtle is not. The sinus and atria of both animals are abundantly supplied with inhibitory fibers.

Technical difficulties have prevented anatomists from drawing accurate conclusions as to the distribution of the cardiac innervation. Recently, Nonidez<sup>20</sup> using a special histologic technic gave a detailed account of the distribution of the cardiac nerves in dogs. The parasympathetic fibers can be traced to their ter-

17 Lewis, T. The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, 1925.

18 Puddu, V. Concerning the Action of Cardiac Nerves, Arch f d ges Physiol **238** 467, 1937.

19 Garrey, W. E., and Bass, G. Effect of Acetylcholine on Frog's Ventricle, Am J Physiol **119** 314, 1937.

20 Nonidez, J. F. Studies on Innervation of the Heart, Am J Anat **65** 361 1939.

minations in the auricles, the bulk of these fibers ending in structures above the coronary sulcus. The sympathetic nerves are distributed as follows. The superior sympathetic nerve does not reach the heart proper, ending in the walls of the large arteries. The middle cardiosympathetic nerve is the largest one in the dog, supplying chiefly the ventricles. The inferior sympathetic nerve, when present, carries afferent fibers from various parts of the heart.

In the present studies data regarding the innervation of the human heart were obtained from the following observations: (1) the effect of pressure on the carotid sinus on ectopic beats arising in the auricles and ventricles, (2) the effect of pressure on the carotid sinus on the auricular and the ventricular rate in complete heart block, and (3) the effect of sympathetic stimulation (epinephrine) on cardiac rhythmicity.

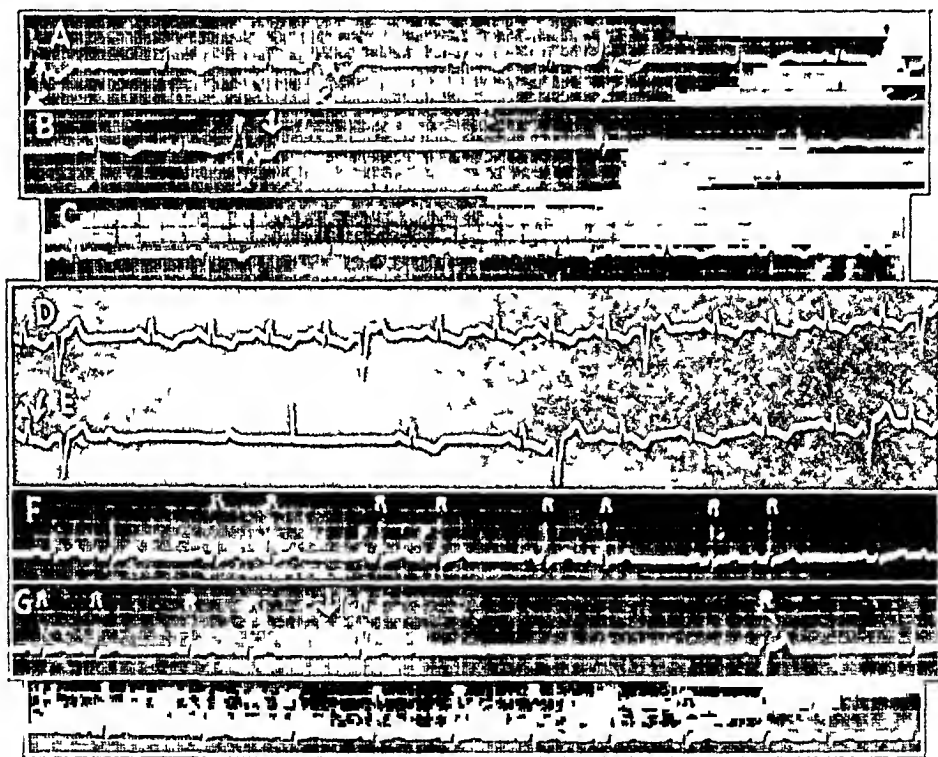


Fig 2—*A*, *B*, and *C*, electrocardiograms made on 1 patient. *A*, consistent rhythm in this patient, cycles of two normal beats followed by a ventricular extrasystole (*X*). *B*, the effect of pressure on the right carotid sinus (arrow), followed in *C* by the abolition of the extrasystoles. *D*, consistent rhythm in another patient, cycles of four normal beats followed by ventricular extrasystole. *E*, an electrocardiogram made on the patient in *D*, showing the short standstill induced by pressure on the carotid sinus followed immediately by a return of the previous rhythm. *F*, coupled beats of auricular origin. *G*, a short standstill induced by pressure on the right carotid sinus (arrow) followed in *H* by elimination of the arrhythmia.

#### EFFECT OF PRESSURE ON THE CAROTID SINUS ON ECTOPIC RHYTHMS

Subjects were selected in whom a definite cardiominhibitory effect could be demonstrated by pressure on the carotid sinus during the period of normal rhythm and in whom ectopic beats occurred. Only those persons were studied in whom the ectopic beats appeared frequently and with definite consistency. Of 25 subjects in whom the ectopic beats were ventricular in origin, pressure on the carotid sinus eliminated the ectopic beats in 5 (fig 2 *A*, *B* and *C*). In the remaining 20 the ventricular extrasystoles were not influenced (fig 2 *D* and *E*). In 4

subjects in whom the ectopic beats originated in the auricle, pressure on the carotid sinus eliminated the ectopic beats (fig 2 F, G and H)

#### EFFECT OF PRESSURE ON THE CAROTID SINUS ON THE RATES OF THE AURICLES AND THE VENTRICLES IN COMPLETE HEART BLOCK

It is usually stated that the ventricular rate in complete heart block is unaffected by such stimuli as increased activity and emotional excitement, indicating that the idioventricular center is much less under nervous control than is the sinus node. Puddu,<sup>19</sup> however, concluded that stimulation of the vagus nerve slowed the ventricular rate in experimental heart block in dogs. He attributed this effect to a transmission of the cholinergic material liberated in the auricles. Cullis and Tribe<sup>21</sup> demonstrated that sympathetic stimulation increases both the auricular and the ventricular rate in experimental heart block but that parasympathetic stimulation did not influence the ventricles. Gilchrist<sup>22</sup> concluded that in human beings the ventricles in heart block are influenced by activity and induced pyrexia and that the ventricular rate may be increased by atropine and epinephrine.

In the present study the effects of reflex stimulation of the vagus nerve were observed in 6 patients who had complete auriculoventricular dissociation. The

#### *Effect of Pressure on the Carotid Sinus on the Auricular and the Ventricular Rate in Complete Heart Block*

Patient	Auricular Rate	Ventricular Rate	After Pressure on the Right Carotid Sinus		After Pressure on the Left Carotid Sinus	
			Auricular Rate	Ventricular Rate	Auricular Rate	Ventricular Rate
N S	80	38	32	35	40	38
H D	88	30	45	30	62	0
M P	118	25	84	25	70	25
M W	100	34	76	34		
H K	64	33	37	33	36	30
C W	65	20	44	29		

results have been tabulated (see table). In each case pressure on the carotid sinus resulted in a definite slowing of the auricular rate. Pressure on the right carotid sinus was followed by a greater effect on the auricular rate in 3 of the 4 patients in whom both carotid sinuses were compressed. In 1 patient (M P) pressure on the left carotid sinus resulted in the more intense auricular inhibition. In none of the 6 patients did pressure on the right carotid sinus effect the ventricular rate. In 3 of the 4 patients in whom both carotid sinuses were compressed there was no effect on ventricular rate after pressure of the left carotid sinus, while in 1 patient (H K) there was a slowing of the ventricular rate from 33 to 30 beats per minute (fig 3). This group of patients having two pacemakers working independently permits the study of the influence of parasympathetic stimulation on each pacemaker. The results support the concept that while the sinus node is profoundly influenced by parasympathetic stimulation, there is little or no effect on idioventricular centers in the human heart. This does not conclusively prove the absence of parasympathetic fibers to ventricular foci. It is possible that the degenerative lesion causing the heart block may also include the

<sup>21</sup> Cullis, W. E., and Tribe, E. M. Distribution of Nerves in the Heart. I. *Physiol* 46: 141, 1913.

<sup>22</sup> Gilchrist, A. R. The Action of Atropine in Complete Heart Block, *Quart J Med* 2: 483, 1933, The Effect of Bodily Rest, Muscular Activity and Induced Pyrexia in Complete Heart Block, *ibid* 3: 381, 1934.

parasympathetic nerve endings, accounting for the lack of response to reflex stimulation of the vagus nerve

#### EFFECT OF SYMPATHETIC STIMULATION ON CARDIAC RHYTHMICITY

It has repeatedly been shown that the rhythmic property of the heart may be disturbed by stimulation of the sympathetic nerves. In previous studies<sup>6</sup> it was found possible consistently to induce cardiac irregularities in human subjects by the administration of 0.1 mg of epinephrine hydrochloride intravenously. The onset of the arrhythmia occurred within one minute after the administration of the drug, and the effect was usually completed within four or five minutes. In every case the ectopic rhythm induced was predominantly ventricular in origin. In some subjects an occasional auricular ectopic beat was noted as the effect of the drug was subsiding. At the height of the reaction the ectopic beats were entirely ventricular in origin.

The combined effect of parasympathetic and sympathetic stimulation on the rhythmic property of the heart has also been studied. Rothberger and Winterbeig<sup>3</sup> demonstrated in dogs that stimulation of the right vagus nerve depressed the sinus node, resulting in a cardiac standstill. If at the same time the left

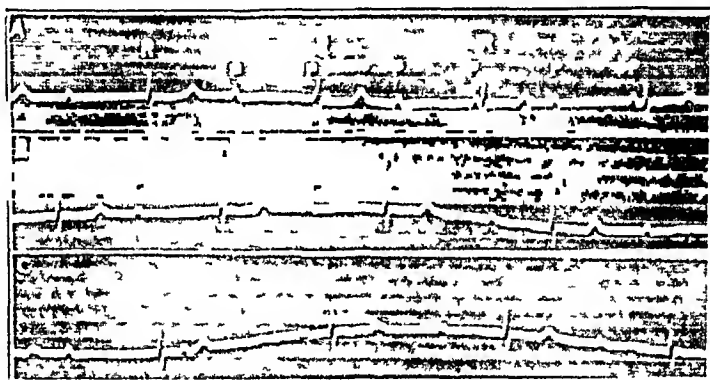


Fig 3—A, complete heart block, auricular rate 64 and ventricular rate 33. B, the effect of pressure on the right carotid sinus, reduction of the auricular rate to 33 and no change in the ventricular rate. C, the effect of pressure on the left carotid sinus, reduction of the auricular rate to 36 and the ventricular rate to 30.

sympathetic nerve was stimulated, the standstill was prevented by the development of new rhythmic centers in the ventricles. I have carried out similar studies on human subjects.<sup>23</sup>

Epinephrine and related compounds were administered to a large number of subjects in whom a cardiac standstill could be induced by pressure on the carotid sinus, and the pressure on the carotid sinus was repeated. In only an occasional instance was the standstill abolished by the restoration of the function of the sinus node. In most cases the standstill was abolished by the development of beats from a ventricular center (fig 4). As an illustration, p-hydroxy- $\alpha$ -methylphenylamine hydrobromide (paredrine hydrobromide)—a sympathomimetic amine—was administered to 14 subjects in whom a cardiac standstill could be induced. In 7 instances the standstill was abolished by the development of a rhythm arising in or near the auriculoventricular node. In 3 subjects lower ventricular centers became active. In 1 subject the rhythm consisted of beats arising from the sinus

<sup>23</sup> Nathanson, M. H. Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, *Arch Int Med* 51:387 (March) 1933, Further Observations on the Effect of Drugs on Induced Cardiac Standstill, *ibid* 54:111 (July) 1934.

node alternating with beats arising from an ectopic ventricular focus, while in 3 instances the sinus node retained its activity. These observations indicate that while the auricles may be influenced to some degree, the predominant effect of sympathetic stimulation is an increase in the rhythmicity of the ventricles. It may be concluded that parasympathetic stimulation depresses the rhythmic property of the human heart, with the predominant effect on auricular rhythmic foci. In some persons, however, ventricular foci may be depressed. The effect of sympathetic stimulation is an increase in rhythmicity predominantly of the ventricles. It is apparent, then, that in states of increased cardiac rhythmicity

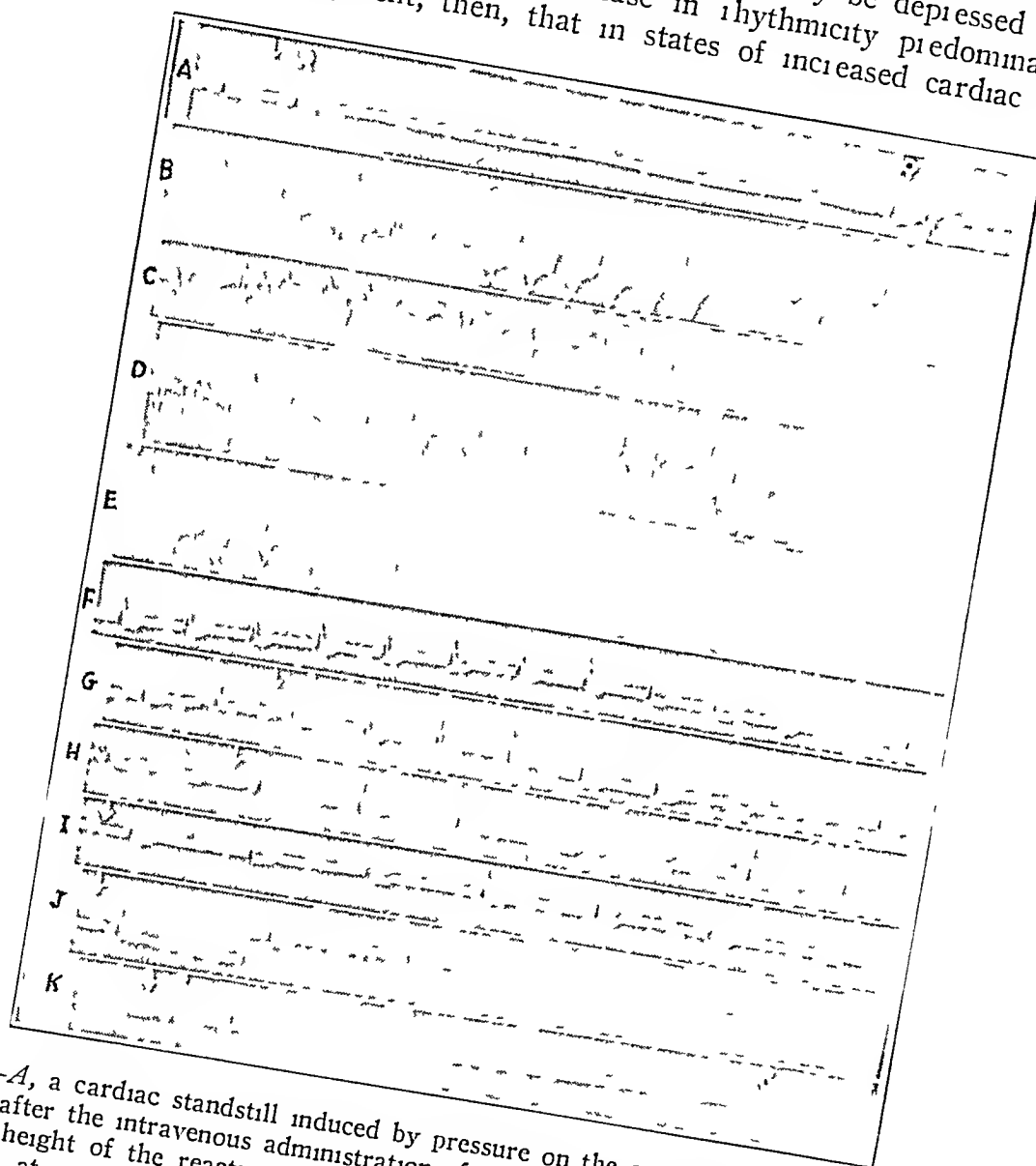


Fig 4—A, a cardiac standstill induced by pressure on the carotid sinus. The lower strips were made after the intravenous administration of 0.2 mg of epinephrine hydrochloride. Note that at the height of the reaction (B through E) the beats arise from multiple, lower ventricular foci at a rapid rate. As the reaction subsides (F through K), the standstill is abolished by the development of a rhythm arising in the auriculoventricular node (ectopic tachycardias) reflex stimulation of the vagus nerve (pressure on the carotid sinus) is most likely to be effective when the ectopic focus is in the auricles. However, this procedure should also be attempted when the ectopic stimulation is ventricular, as the present observations indicate that parasympathetic stimulation depresses ventricular rhythmicity (ventricular standstill). It is also apparent that in states of depressed ventricular rhythmicity, since this predominantly influences the rhythmic function of ventricular foci.



## ACTION OF DRUGS ON REFLEX VAGAL INHIBITION OF THE HEART

The action of drugs which act on the vagus nerve was studied. In 5 subjects in whom a prolonged cardiac standstill could be induced by pressure on the carotid sinus the administration of atropine sulfate, 2 mg subcutaneously, abolished the effect (fig 5). A comparison of figures 5 and 7 demonstrates the difference in the action of atropine and epinephrine. Both drugs abolish the standstill. Atropine, however, merely paralyzes the carotid sinus reflex, and pressure on the carotid sinus does not produce any effect. After medication with epinephrine the reflex continues to function, eliminating the sinus node, but the standstill is abolished by the development of a rhythm from a new pacemaker.

The effect of digitalis was observed in many subjects. Although not entirely consistent an increase in the cardiac inhibition has been the usual reaction. It was noted frequently that in persons who do not show any response to pressure on the carotid sinus a definite reaction will follow digitalization. The results have not been sufficiently consistent to permit the use of the carotid sinus reaction as an accurate indication of digitalization. However, in many instances adequate digitalization was associated with a definite increase in the response to pressure

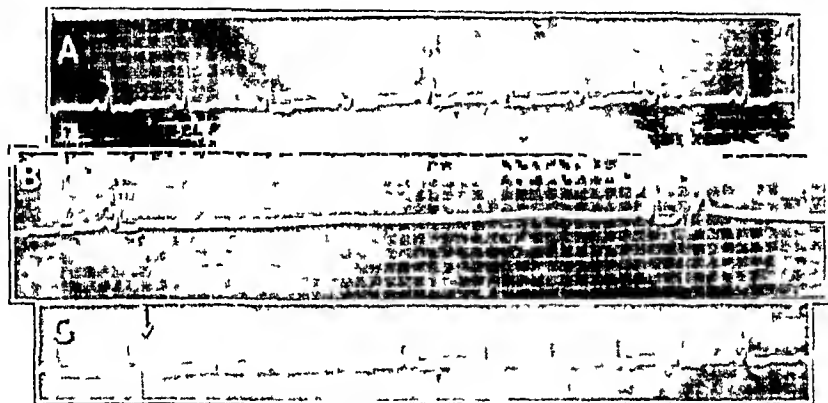


Fig 5 (patient H B, lead II) — *A*, a control electrocardiogram made before pressure was applied to the carotid sinus. *B*, cardiac standstill induced by pressure on the right carotid sinus (arrow). The interval *R-R* is seven and two-tenths seconds. *C*, the abolition of the reflex after the administration of 2 mg of atropine sulfate.

on the carotid sinus. In 1 person having a hyperactive reaction the maximum period of standstill which could be induced on many trials was nine seconds. After digitalization a standstill of fifteen seconds followed pressure on the carotid sinus.

The administration of quinidine to subjects showing a hyperactive response was approached with caution. Since it has been shown that the drug depresses the myocardium and retards the rate of the sinus node in dogs,<sup>24</sup> it seemed possible that this might lead to a further delay in the return to activity of the sinus node resulting in a seriously prolonged cardiac arrest. The drug was thus administered in small and increasing doses. The rather unexpected response after increasing the amount of quinidine sulfate to 2 Gm in divided doses was a definite lessening of the vagus effect, so that the standstill was abolished (fig 6). The explanation of this reaction was clear from the work of Lewis and his associates,<sup>24</sup> who demonstrated that in addition to the direct effect on the myocardium quinidine possesses a definite vagoparetic action. Dale<sup>25</sup> showed that effect of the vagus

<sup>24</sup> Lewis, T, Drury, A N, Ihescu, C C, and Wedd, A M. Observations Relating to the Action of Quinidine on the Dog's Heart, *Heart* 9 55, 1921.

<sup>25</sup> Dale, H H. Note on the Reversal of Vagus Action by Quinidine as Seen in the Heart of the Cat, *Heart* 9 87, 1921.

nerve on the sinus node was not only eliminated by quinidine but that a reversal of the action of this nerve was obtained, with an acceleration of the sinus rate. The vagoparetic effect of quinidine undoubtedly accounts for its failure to be effective in slowing the sinus rate in simple tachycardia. This antagonism between the actions of quinidine and stimulation of the vagus nerve is of practical importance in the therapy of attacks of ectopic tachycardia. If quinidine is administered first and fails to terminate an attack, stimulation of the vagus nerve attempted subsequently either mechanically or chemically will undoubtedly be ineffectual. If both therapeutic procedures are considered, it is apparent that stimulation of the vagus nerve should be attempted before quinidine is administered.

#### ACTION OF DRUGS ON CARDIAC RHYTHMICITY

Pharmacologic studies dealing with the influence of drugs on the rhythmic property of the heart are relatively few and are limited chiefly to laboratory studies on experimental animals. In view of variations in the reaction in different animal species, studies of the response of the human heart are of particular interest. Observations were carried out on the action of drugs on a state of depressed rhythmicity (induced by pressure on the carotid sinus) and increased rhythmicity

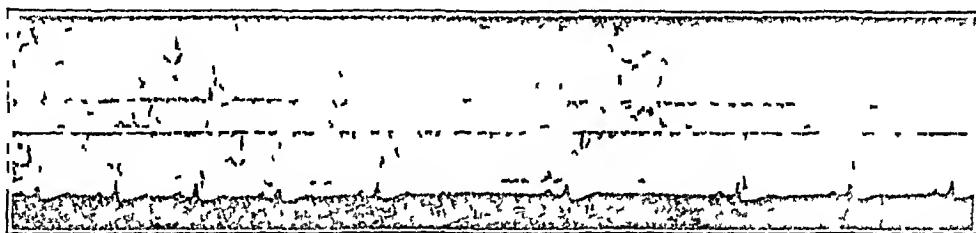


Fig 6—A, a standstill of nine seconds induced by pressure on the carotid sinus (arrow). B, the effect of pressure on the carotid sinus (arrow) after the administration of 2 Gm of quinidine sulfate in divided doses.

(induced by intravenous injection of epinephrine) in a group of human subjects. A summary of these observations follows.

*Effect of Drugs on Depressed Cardiac Rhythmicity*—The technic of these experiments was simple. Subjects, usually elderly men, were selected in whom a prolonged cardiac standstill could be induced consistently by pressure on the carotid sinus. After a control electrocardiogram was taken showing the induced standstill, the drug to be studied was administered and the procedure repeated at suitable intervals.<sup>23</sup> If a drug had no influence in increasing rhythmicity, the cardiac standstill was not affected. If a drug was effective, the cardiac standstill was abolished by the development of a rhythmic focus. The drugs selected for study were compounds which have been recommended in the therapy of cardiac standstill. These included epinephrine hydrochloride, ephedrine sulfate, barium chloride, calcium gluconate, digitalis, caffeine, nikethamide (a 25 per cent solution of pyridine betacarboxylic acid diethylamide), metrazol and thyroxin.

Of this group, it was found that the cardiac standstill could be consistently induced after the administration of barium chloride, calcium gluconate, digitalis, caffeine, nikethamide, metrazol and thyroxin, indicating that these drugs had no stimulating effect on cardiac rhythmicity. After epinephrine and ephedrine the cardiac standstill was consistently abolished, usually by the development of a new

rhythmic focus in the ventricles (fig 7) A group of compounds related to epinephrine was then studied This included ephedrine sulfate, dextroepinephrine bitartrate, cobefrine, adrenalone, epinine, synephrin tartrate, neo-synephrin hydrochloride, tyramine sulfate, hordenine sulfate, phenylethanolamine sulfate and paredrine hydrobromide It was found that all of these compounds (sympathomimetic amines) increased cardiac rhythmicity leading to the prevention of abolition of cardiac standstill Epinephrine was the most effective substance and paredrine the most active stable and orally active compound These observations indicate that increase in the rhythmic property of the heart in those states in which this function is depressed or absent can be obtained only by drugs which have a specific pharmacodynamic action, that of stimulation of the sympathetic innervation of the heart Drugs which do not possess this action are not effective and are not indicated in the treatment or prevention of cardiac standstill

#### ACTION OF DRUGS ON INCREASED CARDIAC RHYTHMICITY

The rhythmic property of the heart was increased by the intravenous administration of epinephrine As mentioned before, this procedure raises ventricular rhythmicity, so that for a time the normal rhythm is almost entirely replaced

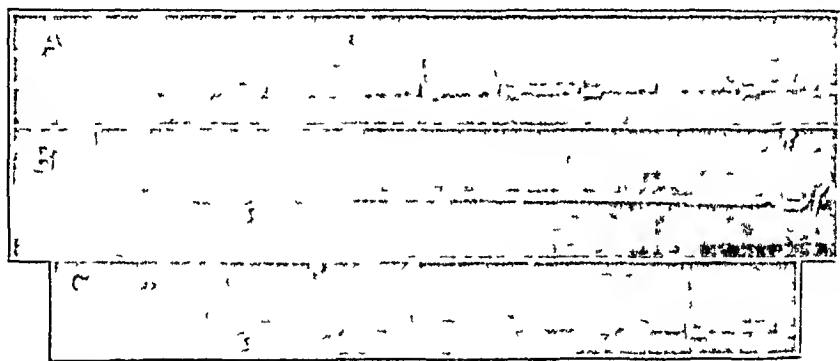


Fig 7 (patient H B, lead II) —A, a control electrocardiogram made before pressure was applied to the carotid sinus B, a standstill induced by pressure on the carotid sinus The interval R-R is seven and five-tenths seconds C, the effect of pressure on the carotid sinus after the administration of epinephrine hydrochloride, 1 mg subcutaneously The standstill is abolished by the development of an idioventricular rhythm These tracings were made on the same patient as those shown in figure 5, and the differences in the effect of atropine and of epinephrine are to be noted

by beats originating in the ventricles The experiments were carried out in the following manner A control electrocardiogram was made and epinephrine hydrochloride, 0.1 mg, was injected intravenously A continuous electrocardiogram was then made until the reaction subsided Those subjects in whom frequent ventricular extrasystoles developed were used for further study Several drugs were administered to these subjects, and at a suitable time the same dose of epinephrine was repeated After the administration of ergotamine, potassium acetate and sodium amytal ventricular rhythms were induced by epinephrine similar to those observed prior to the administration of the drug The reaction was modified in 10 subjects after the oral administration of quinidine sulfate, 1 to 2 Gm, in divided doses In 8 instances the second administration of epinephrine did not induce extrasystolic rhythms, and in 2 subjects only an occasional ventricular extrasystole appeared

It seemed important to investigate the effect of parasympathetic stimulation on increased cardiac rhythmicity Mecholyl chloride was administered to 6 subjects in whom ventricular rhythms could be induced by epinephrine The dose

of mecholyl chloride was 20 mg injected subcutaneously. The second dose of epinephrine was administered five minutes later. In 5 of 6 subjects the ventricular rhythm was almost completely prevented after the administration of the mecholyl chloride (fig 8). These observations are of interest since they indicate that a structure which receives little or no parasympathetic innervation (the human ventricle) is affected by a cholinergic substance. Garrey and Bass<sup>19</sup> concluded that acetylcholine has no influence on structures which do not receive parasympathetic innervation. However, Nahum and Hoff<sup>4</sup> prevented experimental ventricular fibrillation with mecholyl chloride, and these observers<sup>26</sup> also suppressed ventricular rhythms induced in cats by epinephrine hydrochloride with this drug. Starr<sup>27</sup> studied the effect of mecholyl chloride in only 1 patient having frequent ventricular extrasystoles, and the ectopic beats were greatly diminished in fre-

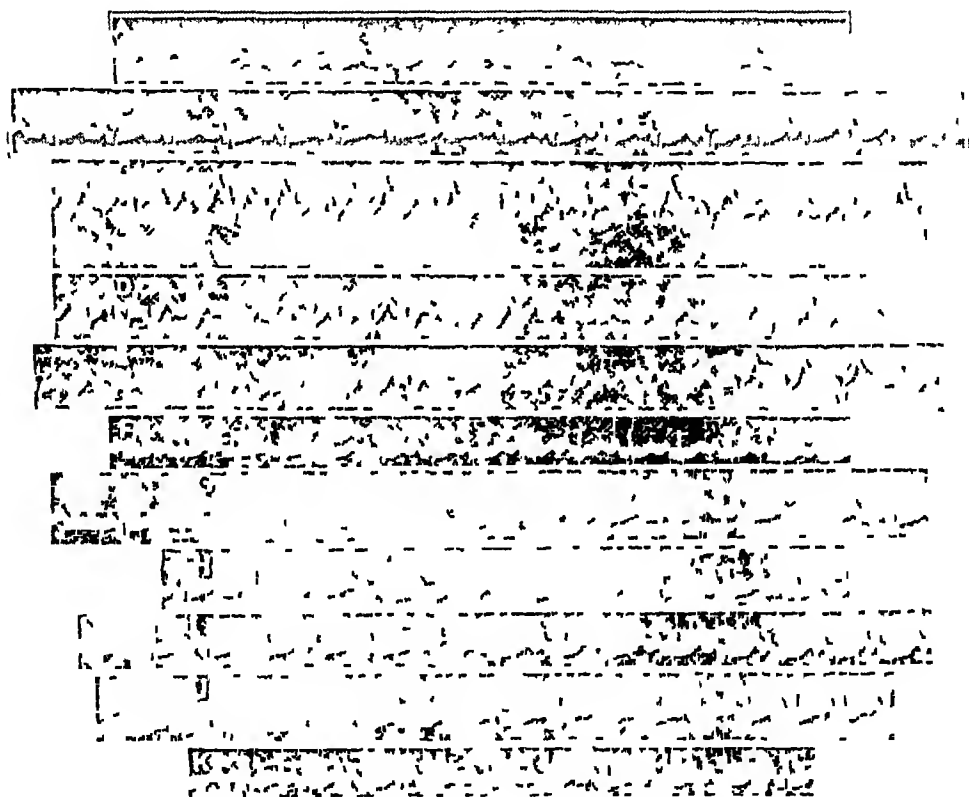


Fig 8—A, a control electrocardiogram made before the administration of epinephrine hydrochloride, 0.1 mg intravenously. B through F, tracings made after medication with epinephrine hydrochloride. Ectopic ventricular beats from multiple foci appear in C, D and E. G, a control electrocardiogram made on the same patient before the administration of mecholyl chloride and epinephrine hydrochloride. H, tracing made after the administration of 20 mg of mecholyl chloride. I, J and K, absence of ectopic beats after the administration of 0.1 mg of epinephrine hydrochloride intravenously.

quency. Although mecholyl has been suggested in the treatment of ectopic rhythms arising from a supraventricular focus, these observations suggest that it does have an influence on ventricular rhythmic foci.

26 Hoff, H. E., and Nahum, L. H. The Role of Adrenaline in the Production of Ventricular Rhythms and Their Suppression by Acetyl- $\beta$ -Methylcholine Chloride, *J. Pharmacol. & Exper. Therap.* 52: 235, 1934.

27 Starr, I., Jr. Acetyl- $\beta$ -Methylcholine. IV. Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm, *Am. J. M. Sc.* 191: 210, 1936.

## SUMMARY

The clinical importance of the rhythmic property of the heart is emphasized

Physiologic and pharmacologic studies are reported on the rhythmic function of the human heart, carried out by modifying the cardiac innervation in the following manner (1) parasympathetic stimulation by pressure on the carotid sinus or administration of mecholyl chloride, and (2) sympathetic stimulation by the administration of epinephrine and related compounds

Reduction in cardiac rhythmicity by parasympathetic stimulation is more marked in males and in persons of advanced age. A hyperactive vagal inhibition of the heart is frequent in patients having coronary disease.

Studying persons in whom the sinus node can be eliminated for comparatively long periods leads to the conclusion that the rhythmic efficiency of ectopic centers of the human heart is low.

Parasympathetic nerves supply mainly rhythmic foci in the auricles, although the ventricles are influenced in some persons by parasympathetic stimulation. Sympathetic stimulation increases the activity predominantly of ventricular foci.

Digitalis increases reflex vagal inhibition of the heart in many persons. Atropine and quinidine have a vagoparetic action.

In states of depression or absence of the rhythmic function (cardiac or ventricular standstill) the only drugs which effectively increase cardiac rhythmicity are those which stimulate the sympathetic innervation (sympathomimetic amines).

Quinidine and mecholyl chloride tend to suppress the increased ventricular rhythmicity induced by epinephrine.

658 South Bonnie Brae Avenue

# DIAGNOSIS OF LIPOID PNEUMONIA BY ASPIRATION BIOPSY

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Within the past fifteen years lipid pneumonia has been repeatedly reported in the literature. In almost every reported instance the diagnosis was a pathologic one made on autopsy material. In an occasional case the diagnosis was suggested by the history and the clinical findings, and the subsequent improvement followed discontinuance of the use of various oral and nasal oils<sup>1</sup>. In rare instances oil droplets have been visualized bronchoscopically and the diagnosis made in that way. It occurred to us that biopsy of material aspirated from the lungs, a procedure now in use in the study of obscure pulmonary and mediastinal lesions, would be of value, and we were successful in corroborating the suggested roentgenographic diagnosis of lipid pneumonia in 5 of 10 cases examined in this way. As far as we can determine, this is the first report of lipid pneumonia demonstrated by aspiration biopsy.

## REPORT OF CASES

CASE 1—G B, a white man aged 82, when admitted to this hospital on July 28, 1941 had a history of rheumatoid arthritis of thirty years' duration. The history was obtained from the daughter, as the patient was hard of hearing. Swelling of joints and pain in both large and small joints marked the beginning of the disease. The course was that of chronic progressive atrophic arthritis involving gradually first the small joints and then the larger ones, including the vertebral joints. The patient became increasingly rigid, and during the last five years was in a wheel chair or confined to bed. He was treated with large doses of morphine sulfate for pain. After admission, the doses of morphine sulfate were gradually decreased, and finally the analgesic was given only sporadically. This patient was given liquid petrolatum, 1 ounce (30 cc) daily, from the time of admission. On July 8, 1942 he had an episode of coughing with slight dyspnea and had a temperature as high as 103 F. Clinically, subcrepitant rales were heard over both bases of the lungs, but there was no dulness. The roentgen examination revealed infiltration of the lower lobes of both lungs, most evident in the mesial and basal portions of the lower lobe of the right lung. Extensive productive and fibrotic changes were present throughout the lower halves of both pulmonary fields. The pathologic observations impressed us as indicating bilateral bronchopneumonia superimposed on chronic pulmonary interstitial fibrosis (fig 1A).

The patient was treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and improved rapidly. Three weeks later he again had fever, cyanosis and cough. There was slight dulness with indefinite rales at both pulmonary bases. A roentgen study made at this time was not entirely satisfactory but showed no change from the previous study. Again sulfathiazole was given, and the patient improved after several days. One month later, in the course of our investigation of patients receiving liquid petrolatum, another roentgen study revealed findings identical with those of the original study. The observations now impressed

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From the departments of pathology and roentgenology of the Jewish Sanitarium and Hospital for Chronic Diseases.

1 Tchekoff, I G, and Ornstein, G G. Bronchopulmonary Disease Attributed to the Use of Intranasal Instillation of Oily Substances, *Quart Bull, Sea View Hosp* 1 139-160 (Jan) 1936. Greenwald, H M, Nathanson, L, and Steiner, M. Chronic Pneumonia Associated with Nutritional Disturbances in Infants, *Am J Roentgenol* 35 454-467 (April) 1936.

us as indicating low grade chronic pneumonic infiltration, and the possibility of lipoid pneumonia was suggested. A subsequent aspiration biopsy confirmed the diagnosis of lipoid pneumonia (figs 2 and 3).

The pneumonic lesion in case 1 was first demonstrated during the acute respiratory infection and persisted after the temperature subsided. The lesion was again demonstrated on the routine follow-up of patients' receiving large quantities of liquid petrolatum. It was then our impression that this patient had undergone an infection of the upper respiratory tract which did not alter the roentgen findings that were present at the first study.

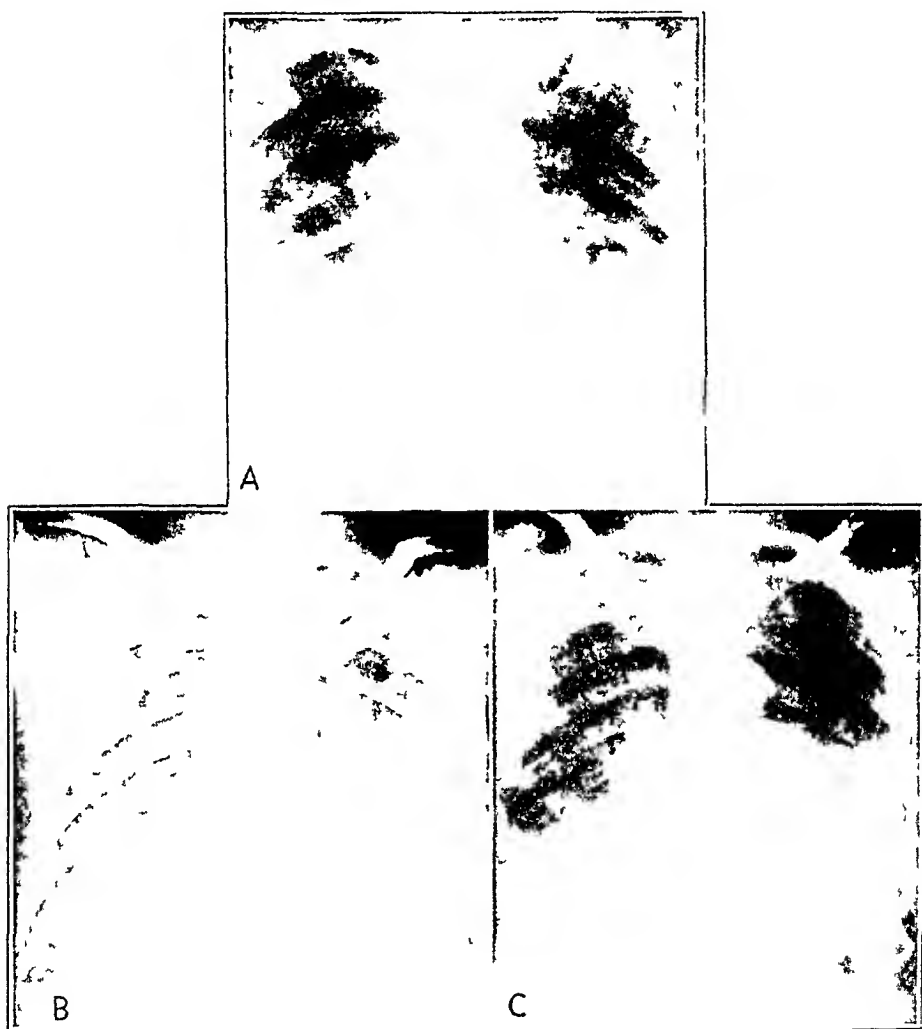


Fig 1—*A*, infiltration of the lower lobes of both lungs in case 1. The infiltration is most intense in the mesial and basal portion of the lower lobe of the right lung. Note the diffuse fibrosis. *B*, consolidation of the lower lobes of both lungs in case 2, most dense in the mesial portions of the lung fields. *C*, essentially normal bronchi, shown by passive bronchoscopy in case 2.

**CASE 2**—S W, a 58 year old man, was admitted to this hospital on Sept 11, 1931. Six weeks prior to his admission he had suffered cerebral thrombosis resulting in left hemiplegia. Prior thereto the patient had apparently been in good health. Until Feb 19, 1940 he was ambulatory. On that day he experienced cerebral thrombosis resulting in paresis of the right side with aphasia. The picture was that of pseudobulbar palsy. There was great difficulty in swallowing, and his speech was dysarthric. The patient had been receiving liquid petrolatum since 1935, when he complained of constipation following acute enteritis with diarrhea. He received about 1 ounce (30 cc) of liquid petrolatum two to three times weekly for about three years. Since the second cerebral episode (February 1940)

he had been taking 1 ounce of liquid petrolatum every other night. In August 1940 he had an episode of coughing and dyspnea with temperature ranging from 101 to 103 F. Clinically, there was no dulness, and few subcrepitant rales were heard over the bases of both lungs. A roentgenogram taken at that time revealed dense consolidation of the mesial and basal portion of the lower lobe of the right lung and the lower half of the left lung (fig 1B). The patient was given sulfonamide compounds, and the fever and other symptoms soon subsided. A roentgenogram taken two months later revealed the same changes, and passive bronchography showed no evidence of bronchiectasis (fig 1C). The infiltration was then regarded as interstitial or alveolar in type, and we suggested the diagnosis of lipoid pneumonia. A roentgenogram taken on Nov 3, 1942 revealed essentially the same conditions as the one previous. An aspiration biopsy revealed the typical cells of lipoid pneumonia.

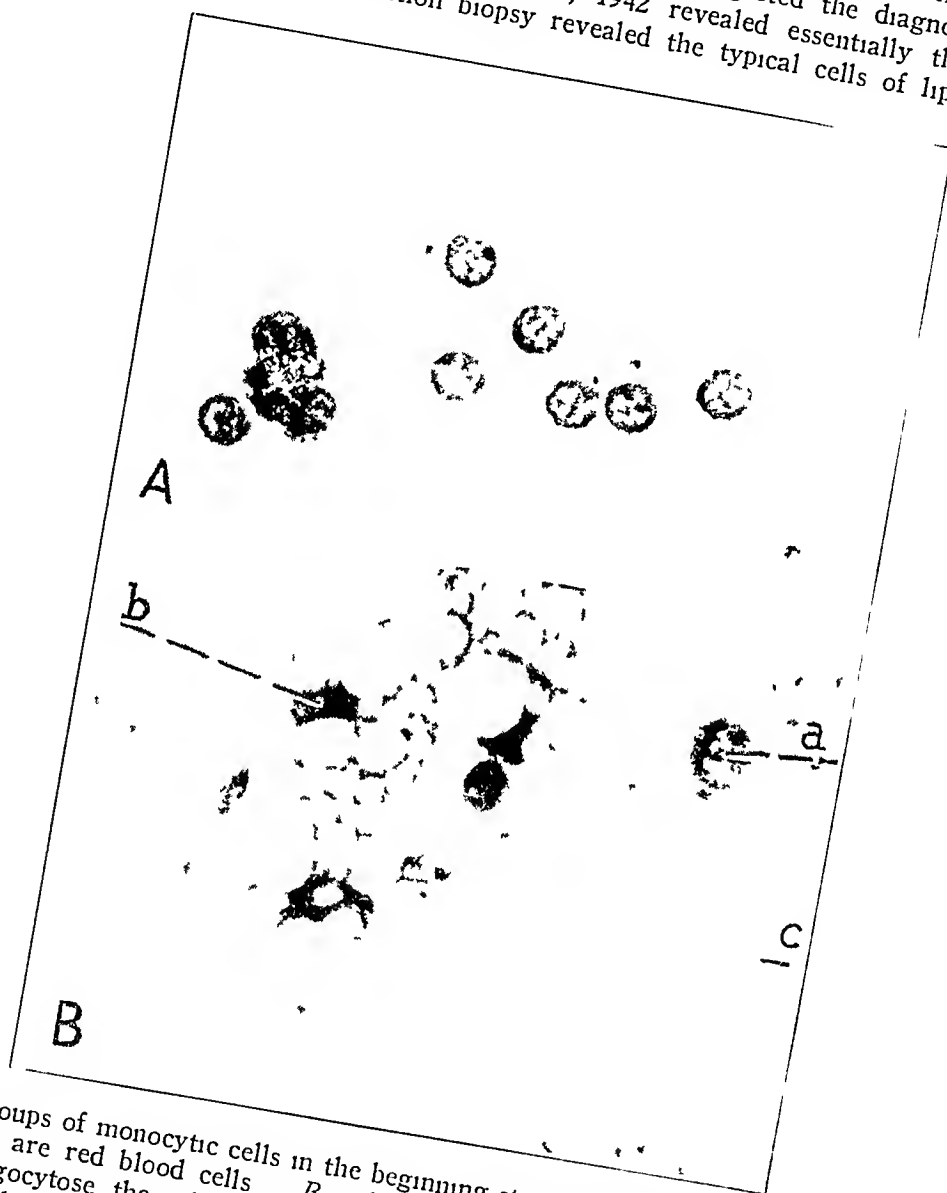


Fig 2—A, groups of monocytic cells in the beginning stage of phagocytosis. The pale round cells at the right are red blood cells. B, cells aspirated from the lungs. (a) macrophages beginning to phagocytose the oil droplets, (b) groups of macrophages in a later stage of inhibition, (c) red blood cell.

The first roentgen study in case 2 was made because of an acute pulmonary episode, which clinically suggested a bilateral pneumonic process. The final roentgen study, made more than two years later, showed no appreciable change, indicating that the infection was low grade. Because the lesion was of a bilateral basal type, the thought was entertained that this was a low grade aspiration type of pneumonia, possibly lipoid in nature. It is impossible to state from the roentgenograms whether this patient had superimposed bronchopneumonia, since there was no change of the pulmonary findings on subsequent films.



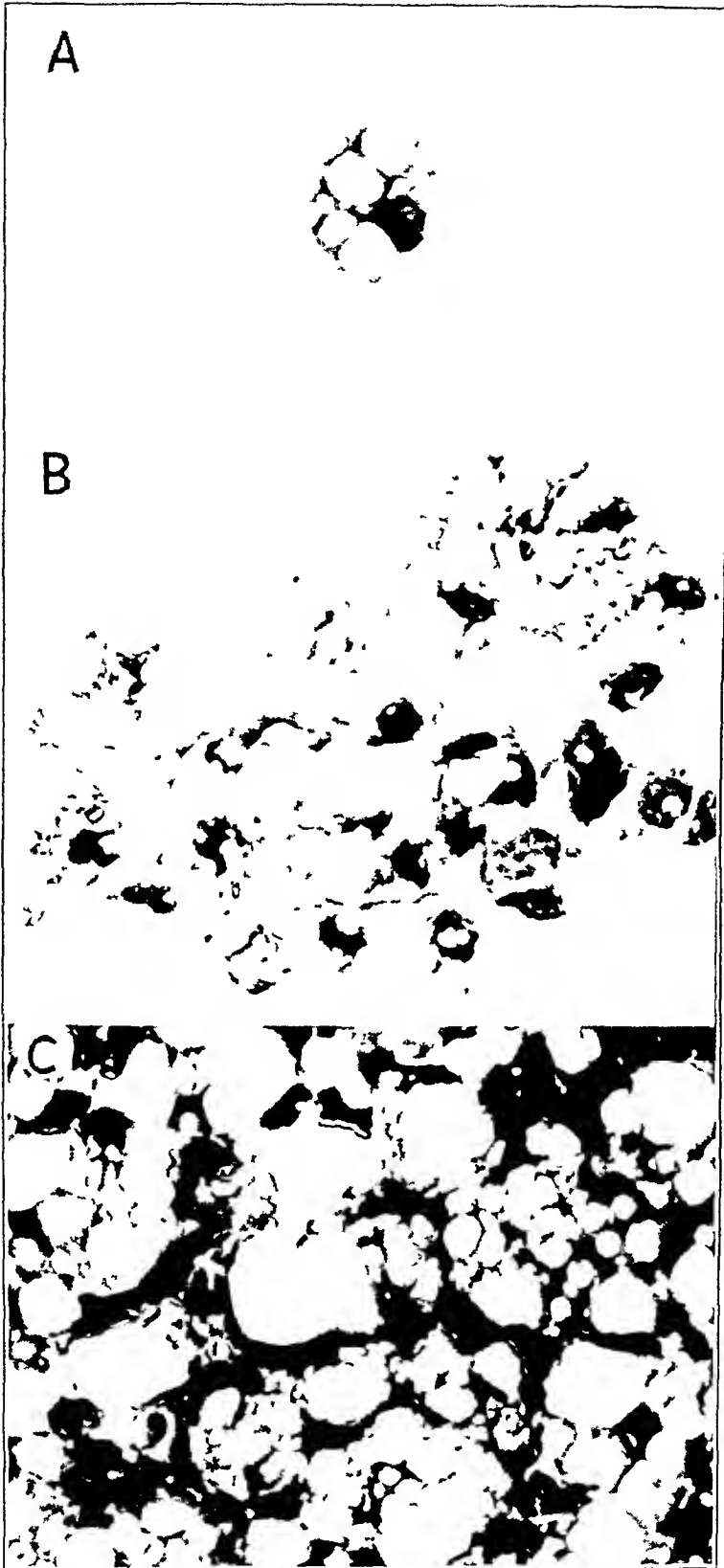


Fig 3—*A*, single lipophagic cell. Note the fine subdivisions of the phagocytosed oil droplets. *B*, stage of disintegration of macrophages. *C*, meshwork of fibrotic tissue with entrapped oil droplets. Formation of giant cells can also be seen.

CASE 3—J P, a 57 year old white woman, was admitted to the hospital on Nov 30, 1937. About eleven years prior to admission it was accidentally discovered that she had hypertension. She had been in fairly good health, complaining only of occasional dizziness. Six weeks prior to admission she had a cerebral episode resulting in left hemiplegia. Speech returned almost completely within two weeks. On admission to this hospital, redundant colon and secondary megacolon were diagnosed. The patient was given liquid petrolatum, 1 ounce (30 cc) daily. A routine roentgen examination of the chest at that time (Dec 16, 1937) gave entirely negative results (fig 4 A). The patient was bedridden at all times. During her stay there were many episodes of fecal impaction, and oil enemas had to be given and manual extraction resorted to. To prevent impaction, many cathartics in addition to liquid petrolatum were given. The patient was dull mentally, but her speech was normal and the ninth and tenth cranial nerves were intact. A routine roentgen examination made Dec 14, 1942 showed irregular coalescence and patchy infiltration of the lower lobes of both lungs. The lesions on both sides were extensive (fig 4 B).

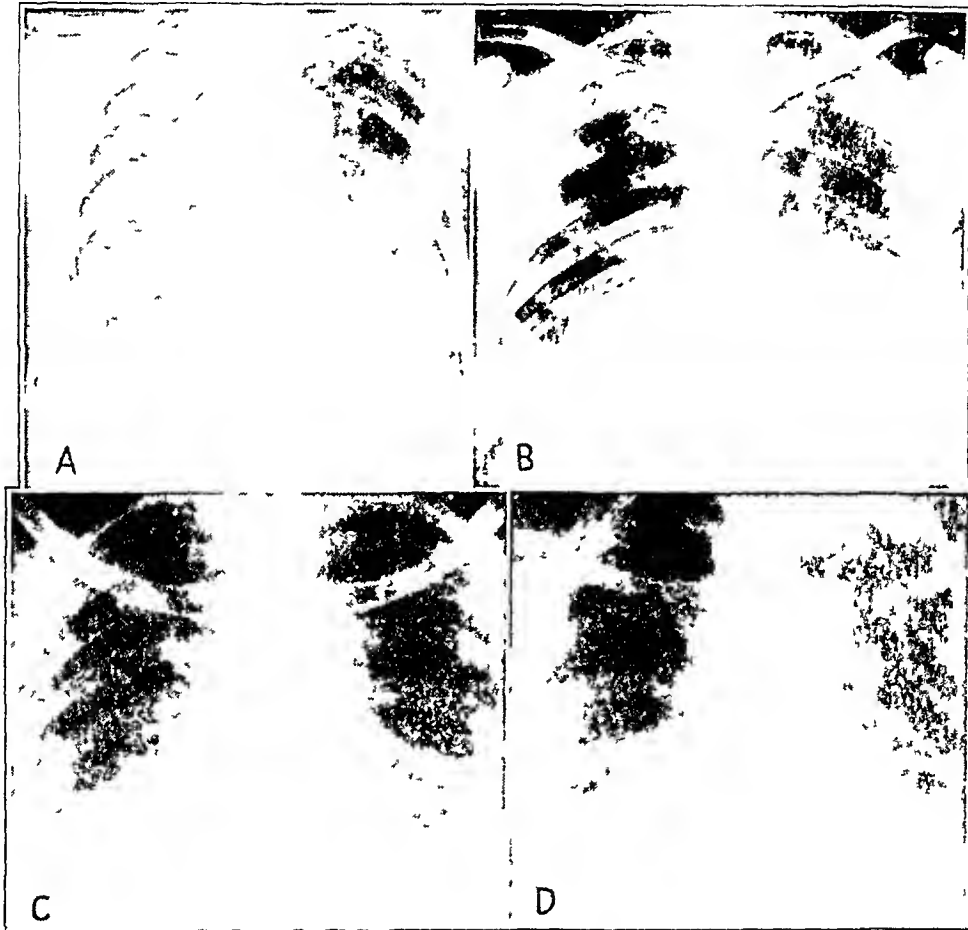


Fig 4—A, normal chest of the patient in case 3 on Dec 16, 1937. B, chest of the same patient on Dec 14, 1942. Note the dense mottled consolidation involving the lower lobes of both lungs, particularly evident in their mesial portions. C, irregular infiltration involving the basal portion of the lower lobe of the right lung in case 4. The infiltration is particularly intense in the mesial and supradiaphragmatic portions. D, dense infiltration adjacent to the border of the heart and patchy infiltration, fibrotic in character, extending through the lower lobe of the right lung in case 5.

In case 3 we were able to follow the patient roentgenographically for a period of five years. The original roentgenographic study of the chest revealed no abnormality. The final one, made during a routine examination of patients receiving considerable quantities of liquid petrolatum, showed the pathologic roentgenographic features described. There were no clinical symptoms or physical signs referable to the chest. A diagnosis of lipoid pneumonia was suggested from the roentgen

studies, and an aspiration biopsy revealed typical vacuolated cells in great masses, patched together. A small amount of fibrosed pulmonary tissue could also be seen on the smears.

CASE 4—S A, a white woman aged 58, was admitted to this hospital in May 1934. Five years prior to admission she had been operated on for disease of the gallbladder, three years later she was operated on because of adhesions. During the last ten years she had suffered from frequent attacks of asthma and of paroxysmal tachycardia. A diagnosis was made of coronary sclerosis, hypertensive heart disease and postoperative adhesions. The patient had received 1 ounce (30 cc) of liquid petrolatum daily since 1934. Many indefinite rales were heard at the bases of the lungs, but there was no dulness. During the asthmatic attack many musical rales were audible throughout both lungs. Signs of cardiac decompensation were not present. A roentgenographic study of the chest in April 1938 showed no abnormality. A study of the chest made Nov 13, 1942 (fig 4C) during a routine investigation of patients receiving liquid petrolatum over a period of time showed a dense irregular infiltrative lesion involving particularly the mesial portion of the lower lobe of the right lung and the most dependent portion of the right lung above the diaphragm. Because of the negative pulmonary history and the negligible physical signs, the diagnosis of low grade aspiration pneumonia, possibly of a lipid type, was suggested. Repeated biopsies revealed the typical cells of lipid pneumonia in various stages.

Although the roentgen studies and the aspiration biopsy clearly indicated the presence of lipid pneumonia, the patient was entirely symptom free except for long-standing asthma. The physical findings were those attributable to the asthma.

CASE 5—B S, a white woman aged 66, was admitted to this hospital in October 1941. She gave a history of hypertension of long standing. In 1916 she had Bell's palsy, which improved on electrical treatment. In 1935 she suffered a cerebral insult resulting in right hemiplegia without aphasia. During that year mild diabetes was discovered. In May 1941 she had a cerebral insult without loss of consciousness, increasing the paralysis on the right side. Physical examination revealed severe hypertension, an aneurysm of the internal carotid artery of the neck and right hemiplegia without aphasia. She had been confined to bed since the second cerebral accident. She had been taking liquid petrolatum for several years because of chronic constipation. A barium sulfate enema revealed diverticula of the large bowel. During her stay in the hospital she received about 1 ounce (30 cc) of liquid petrolatum daily. Again, during the routine investigation of patients receiving liquid petrolatum over a long period, a roentgenogram (fig 4D) of the chest disclosed a dense infiltrative lesion involving the mesial portion of the lower lobe of the right lung adjacent to the heart with patchy areas of infiltration throughout the remainder of the lobe, particularly over the diaphragm. A densely thickened pleura was present along the lower axillary portion of the lung. Because of similar findings in other patients, we again suggested the diagnosis of low grade aspiration pneumonia, and an aspiration biopsy disclosed a lipid type of pneumonia.

#### COMMENT

The positive diagnosis of lipid pneumonia, or, to use a better term, oil aspiration pneumonia, has in the past been a pathologic one. The condition was studied on autopsy material<sup>2</sup> and on animal material in which lipid pneumonia had been produced experimentally.<sup>3</sup> The various reactions of the lung tissue to different oils were first described by Pinkerton,<sup>3a</sup> and he enumerated the following pathologic responses: (a) Animal oil produces fibrosis and giant cell formation in the lung together with necrosis and edema, the latter two depend on the amount of free fatty acids present in the oil. (b) Vegetable oils (e g, poppyseed oil), with the exception of chaulmoogia oil, produce practically no reaction. (c) Liquid

2 Laughlen, G F. Studies on Pneumonia Following Nasopharyngeal Injections of Oil, *Am J Path* **1** 407 (July) 1925. Rabinovitch, J, and Lederer, M. Lipid Pneumonia, *Arch Path* **17** 160-168 (Feb) 1934.

3 Pinkerton, H. (a) The Reaction of Oils and Fats in the Lungs, *Arch Path* **5** 380-401, (March) 1928, (b) Oils and Fats: Their Entrance into and Fate in the Lungs of Infants and Children, *Am J Dis Child* **33** 259-285 (Feb) 1927.

petrolatum (mineral oil) produces a macrophagic reaction with giant cell formation and fibrosis. The largest series of cases was published recently by Freeman and associates<sup>4</sup>. They reported 47 cases—41 which were taken from autopsy material and 6 in which the clinical diagnosis was made on presumptive evidence that warranted the diagnosis of lipid pneumonia.

In our investigation we were primarily concerned with finding and evaluating a means of establishing the diagnosis of lipid pneumonia during life. While pursuing this aim, we were able to observe the evolution of the process hitherto described on autopsy material only.

The histologic response of the lung to liquid petrolatum can be briefly summarized as follows. The droplets of oil entering the alveolar space act as a chemical mechanical irritant. Soon monocyctic cells (fig 2 *A*) appear and phagocytose the oil droplets. At first these cells take on a foamy appearance (fig 2 *B*), later, in the course of imbibition, they resemble ordinary fat cells. At first round or oval, they become bulky and of irregular contour, depending on the number of oil droplets phagocytosed. The latter press the nucleus toward the periphery but retain their subdivision for a long time (fig 3 *B*), possibly until the cell disintegrates (fig 3 *B*). In this stage one finds giant cells and fibrosis—briefly, a histologic response commonly seen in the presence of a foreign body. As time goes on the fibrosis increases, and the oil of the disintegrated lipophages becomes entrapped in the meshwork of the fibrous tissue (fig 3 *C*). If the amount of fat is considerable, and if fibrosis and giant cell formation are so abundant as to form a tumor, one speaks of a paraffinoma. The latter stage was not encountered in our series of cases.

Since the aspiration of the oil in most cases extends over a period of years, one is apt to find all the various stages of lipid pneumonia present concomitantly. This has been proved on autopsy material as well as in our series of aspiration biopsies. Ten patients having a history of taking liquid petrolatum over a period of years were investigated. The patients were selected at random, but the presence of dysphagia or dysarthria or the fact that the patient was bedridden guided us in the choice. After roentgen films of their chests had been taken, those with positive roentgen findings were subjected to aspiration biopsies. Repeated biopsies were made in all cases in order to exclude any doubtful findings and to demonstrate the various stages of the pathologic process. A positive result of an aspiration biopsy was considered of significance but a negative one did not necessarily rule out the diagnosis.

The following technic was used.

The pulmonary lesion was carefully localized in each instance by means of roentgenograms. As a rule, the posteroanterior and lateral views sufficed. Fluoroscopic control was not necessary but may be used if the patient's condition permits. The skin was anesthetized with 2 cc of 1 per cent solution of procaine hydrochloride. A 20 cc syringe with a spinal tap type of needle was used. The plunger of the syringe was withdrawn to the 5 cc mark, and the needle was inserted into the localized area, penetrating as much as 9 to 10 cm, depending on the site of the lesion. Once the needle was inserted, we attempted to withdraw the plunger to make sure the point of the needle was not in a blood vessel or a bronchus. The plunger was then forced down to the bottom of the syringe, ejecting the contents of the lumen of the needle, so as to remove any tissue that may have entered in the passage through the chest wall. The position of the needle was then changed slightly either by withdrawing the needle or by altering its direction. The plunger was then slowly withdrawn with aspiration of as much tissue as possible. Finally, the needle was withdrawn,

4 Freeman, D. G., Engelberg, H., and Merritt, W. H. Oil Aspiration Pneumonia in Adults, *Arch Int Med* 66:11-38 (July) 1940.

and the contents were forcefully ejected on four slides. One slide was regarded as an ordinary blood smear and stained with Wright's stain for ten minutes. The other three were treated with various fat stains for the identification of the type of fat.

The histologic character of the smear depended on the area from which the tissue was aspirated. Usually it was loaded with red blood cells and scattered phagocytic cells, the latter were often in groups of two to three. Occasionally a smear was obtained which contained a rather small number of the macrophages, and occasionally the material consisted of clumps of macrophages, fat droplets, fibrocytes and giant cells. The presence of macrophages in the smear was considered of positive diagnostic value. The fat stains confirmed the character of the phagocytosed material. Because of the rather "blind" selection of the area for aspiration biopsy, it is difficult to state how far the lesion has progressed. Where, however, the roentgen film shows a lesion resembling a tumor, the aspiration should be done under fluoroscopic control so as to obtain tissue directly from the tumefied area. Because of the chronicity of this type of lesion and the probable obliteration of the pleural space, we did not hesitate in using this method of diagnosis. No untoward effects were noticed in any of our patients except 1, who expectorated a small amount of blood. A half-grain (0.03 Gm.) of a codeine salt usually sufficed to control the pain and the anxiety.

Roentgenographically the pulmonary lesion was not characteristic, but the infiltration as a rule involved the lower lobes of both lungs and particularly the lower lobe of the right lung. The mesial portion of the latter lobe adjacent to the heart was the earliest site of involvement. The infiltration then spread to the dependent portions of the lobe above the diaphragm. The process varied in character from patchy infiltration to dense consolidation with fibrosis. There was little change in the lesion over prolonged periods.

#### SUMMARY AND CONCLUSIONS

Ten patients who had a history of receiving liquid petrolatum for many years and who had suggestive roentgenograms pointing toward the diagnosis of lipoid pneumonia were investigated by means of aspiration biopsies. The material aspirated from the lungs of 5 of the 10 patients gave smears containing the characteristic lipoid macrophages.

One patient had difficulty in swallowing. Two had hemiplegia (without dysphagia). Four were bedridden or confined to wheel chairs.

The roentgenographic studies showed the pulmonary lesions confined to the mesial portions of the lower lobes of both lungs and particularly to the lower lobe of the right lung.

The positive smear can be regarded as diagnostic. A negative smear does not rule out the diagnosis.

The technic of an aspiration biopsy of the lung is outlined. No serious ill effects were encountered following this procedure.

The evolution of the pathologic process was followed during life by means of such biopsies.

Drs. A. M. Rabiner, C. Solomon, H. Mandelbaum and L. Lowe, in whose services the cases reported in this paper were studied, gave us permission to report these cases.

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# SYPHILIS

## A REVIEW OF THE RECENT LITERATURE

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AND

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BALTIMORE

The material for this article has been selected from publications which have appeared from July 1942 to June 1943. As in previous reviews,<sup>1</sup> it has been necessary rigidly to select material, excluding comparative serologic studies and most case reports. The number of European journals available for review is negligible, but the deficit is offset by the growing interest of Latin American authors in the subject. Because the war has focused attention on the prevention of syphilis, especially among the armed forces, there is an increased number of articles on control of the disease.

### HISTORY OF SYPHILIS

A fascinatingly readable account of syphilis as disclosed in the writings of the Elizabethan playwrights and pamphleteers has been contributed by Zimmermann.<sup>2</sup> Important historical points are clarified and a vivid picture of daily life in Renaissance Europe depicted. The customs of these times, crude, rough, even bawdy, are portrayed in such a manner as to present not only a clinical but also a public health picture of syphilis as seen by the physicians and public health officials of the day.

Elizabethan England is depicted through the words of Shakespeare, Johnson and the lesser lights. The problems of today (prostitution, pandering, high incidence of syphilis, clinical syndromes of the disease) also confronted physicians centuries ago. Zimmermann is more than a competent historian, he is an excellent entertainer. In his stories of syphilis of a century ago the physician will find information and pleasurable relaxation.

According to Poirier,<sup>3</sup> syphilis was brought to Canada by a sailor who accompanied Jacques Cartier on his first voyage in 1534. A notable epidemic

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From the Syphilis Division of the Medical Clinic, the Johns Hopkins University and Hospital.

1 (a) Moore, J E. Syphilis. A Review of the Recent Literature, *Arch Int Med* **56** 1015 (Nov) 1935. (b) Padgett, P, and Moore, J E. Syphilis. A Review of the Recent Literature, *ibid* **58** 901 (Nov) 1936. (c) **60** 887 (Nov) 1937. (d) Padgett, P, Sullivan, M, and Moore, J E. Syphilis. A Review of the Recent Literature, *ibid* **62** 1029 (Dec) 1938. (e) Moore, J E, and Mohr, C F. Syphilis. A Review of the Recent Literature, *ibid* **64** 1053 (Nov) 1939. (f) Mohr, C F, Padgett, P, and Moore, J E. Syphilis. A Review of the Recent Literature, *ibid* **66** 1112 (Nov) 1940. (g) Mohr, C F, Padgett, P, Hahn, R, and Moore, J E. Syphilis. A Review of the Recent Literature, *ibid* **69** 470 (March) 1942. (h) Reynolds F W, Mohr, C F, and Moore, J E. Syphilis. A Review of the Recent Literature, *ibid* **70** 836 (Nov) 1942.

2 Zimmermann, E L. (a) Syphilis and the Elizabethan Playwrights and Pamphleteers, *Am J Syph, Gonorr & Ven Dis* **27** 78 (Jan) 1943, (b) **27** 226 (March) 1943.

3 Poirier, P. Histoire de la syphilis en Amérique, *J de l'Hotel-Dieu de Montréal* **1** 64 (Jan-Feb) 1943.

occurred about the Bay of St Paul after the introduction of syphilis into the area by a group of soldiers in 1773, and subsequently spread along the St Lawrence and Ottawa rivers and throughout the entire province of Quebec. The true nature of the malady was not recognized by a group of eminent physicians sent by the government to investigate. It was identified as syphilis in 1785 by Philippe Louis Francois Badelard, whose monograph describing his findings is said to have been the first medical publication in Canada.

The mal de la Baie St-Paul has not received the same publicity as the massacre of Lachine or the deportation of the Acadians, but its repercussions were more profound and more pernicious than any other situation faced by the struggling young colony.

#### SPIROCHAETA PALLIDA

*Spirochaeta Pallida in the Electron Microscope*—Knowledge of the morphology of *Spirochaeta pallida* has been furthered through the use of the electron microscope, capable of obtaining very high magnification. Unfortunately technical difficulties necessitate immobilization and desiccation of the organism, so that some distortion is present. Wile, Picard and Kearny<sup>4</sup> note that as seen in the electron microscope *S. pallida* undergoes distortion, lengthening and flattening of the coils ascribable to the technic of preparation. A complete and continuous membrane-like structure about the organism was demonstrated as were knoblike structures of fairly uniform density which seemed to be integrated with the body of the organism.

Although unable to see flagella on *S. pallida* under the electron microscope by direct inspection of the fluoroscopic screen, Wile and Kearny<sup>5</sup> note that flagellum-like processes may be demonstrated in enlarged photographic reproductions. These processes were found frequently enough to justify the assumption that they are an integral part of the organism.

In addition to the demonstration of granules, spherical bodies and flagellum-like filaments, Morton and Anderson<sup>6</sup> have made certain observations on the division of spirochetes. In the electron microscope, these workers have noted initial constriction of the spirochetal body, leading eventually to two spirochetes held together by a tenuous membrane. After separation of the organisms at this point, the thin membrane persists as a terminal filament.

*Cultivation of Spirochetes*—Kast and Kolmer<sup>7</sup> have been unable to cultivate *S. pallida* on an artificial medium containing normal rabbit testicular tissue after the method of Morrison (to whom in 1941 a government patent was issued covering the procedure). It is a remarkable commentary on the United States Patent Office that a patent can be issued for claimed bacteriologic success in this difficult field to a physician who has commercialized "vaccines" and "serums" for syphilis, tuberculosis and, of all things, hypertension. Apparently one can patent anything, whether or not it works.

The differentiation of *S. pallida* from other spirochetes which so frequently are found in the oral cavity, especially when dental hygiene is poor, is a matter of

4 Wile, U J, Picard, R G, and Kearny, E B. Morphology of *Spirochaeta Pallida* in the Electron Microscope, *J A M A* **119** 880 (July 11) 1942.

5 Wile, U J, and Kearny, E B. The Morphology of *Treponema Pallidum* in the Electron Microscope. Demonstration of Flagella, *J A M A* **122** 167 (May 15) 1943.

6 Morton, H E, and Anderson, T F. Some Morphologic Features of the Nichols Strain of *Treponema Pallidum* as Revealed by the Electron Microscope, *Am J Syph, Gonorr & Ven Dis* **26** 656 (Sept) 1942.

7 Kast, C C, and Kolmer, J A. A Note on the Cultivation of *Treponema Pallidum* with the Preservation of Virulence, *Am J Syph, Gonorr & Ven Dis* **27** 309 (May) 1943.

practical importance to the syphilologist. Under the dark field microscope this differentiation may be very difficult. Were cultivation and isolation of oral spirochetes a practicable clinical procedure, more clearcut distinctions might be possible. Wichelhausen and Wichelhausen<sup>8</sup> have been able to obtain pure cultures of spirochetes from fusospirochetal oral lesions. The isolation of these strains was accomplished by filtration through Chamberland-Pasteur filters, by cultivation in deep agar shake tubes and by anaerobic cultivation in the depth of blood agar plates. The morphologic and cultural characteristics of nineteen strains of oral spirochetes are described. Two of these strains were serologically related to each other and to culture strains of organisms (Reiter, Kazan) originally considered to be *S. pallida*.

*Survival in Frozen Plasma*—The rapid increase in the popularity of blood banks throughout the country and particularly the accumulation of large stores of plasma, liquid, frozen or dried, have made important the study of survival of *S. pallida* in these various preparations.

Ravitch and Chambers<sup>9</sup> report that human and rabbit plasma heavily inoculated with *S. pallida* and frozen at  $-20^{\circ}\text{C}$  for forty-eight hours or longer is not infectious for normal rabbits. Such material was infectious, however, when the freezing period was only twenty-four hours. Under these conditions the incubation period is prolonged even though the experimental animals received an inoculation dose twice the size of that given the controls.

*Appearance in the Blood Stream*—The precise time at which *S. pallida* enters the general circulation after inoculation into man is not known. In experimental animals, the organisms have been demonstrated to enter the blood stream within a relatively few minutes. In man, it is commonly taught that spirochetemia develops just prior to the appearance of the secondary lesions.

Evidence that *S. pallida* may invade the blood stream before the lesions of early syphilis appear is furnished by Bickers<sup>10</sup>. This author reports a case of congenital syphilis in a newly born child acquired before the appearance of the primary sore in the mother. The mother was known to have negative serologic reactions for syphilis ten months, one month and two weeks before the chancre developed, and a history of contact with an infected partner twenty-two days before the lesion appeared was established. The chancre became obvious three days post partum and was followed five weeks later by a secondary eruption. At the age of 3 weeks the infant showed lesions of congenital syphilis and had a positive serologic reaction of the blood.

*Treatment-Resistant Strains of S. Pallida*—Further studies on a treatment-resistant strain of *S. pallida* have been reported by Beerman and Severac<sup>11</sup>. When a patient with syphilis fails to respond to the usual antisyphilitic therapy, it is considered that the resistance is due to one or a combination of the following factors: the peculiarities of the host, the potency of the antisyphilitic remedy, and a special biologic peculiarity of the strain of *S. pallida*.

8 Wichelhausen, O. W., and Wichelhausen, R. H. Cultivation and Isolation of Mouth Spirochetes, *J. Dent. Research* **21** 543 (Dec.) 1942.

9 Ravitch, M. M., and Chambers, J. W. Spirochetal Survival in Frozen Plasma, *Bull. Johns Hopkins Hosp.* **71** 299 (Nov.) 1942.

10 Bickers, W. Congenital Syphilis Acquired by Fetus Before Appearance of Chancre in Mother, *Arch. Dermat. & Syph.* **46** 135 (July) 1942.

11 Beerman, H., and Severac, M. The Problem of Treatment-Resistant Syphilis. Further Studies on a Treatment-Resistant Strain of *Spirocheta Pallida*, *J. Invest. Dermat.* **5** 269 (Oct.) 1942.



The opportunity for the present study was afforded by a patient with early syphilis whose early lesions failed to respond to a total of 54 Gm of various arsenicals but did respond to prolonged use of a bismuth compound intramuscularly and nonspecific therapy. The problems considered were, first, the characteristics of the strain of *S. pallida* isolated from this treatment-resistant patient, and second, the comparative effect of arsphenamine treatment on rabbits infected with this strain as compared with rabbits infected with the Nichols-Hough strain.

As the strain studied was carried through successive transfers, it appeared to acquire enhanced virulence for rabbits. At first, the percentage of "takes" was low, the incubation period variable and the lesions atypical. Later, inoculation resulted in characteristic manifestations after a standard period of incubation in a high percentage of animals. Experiments to determine the response to treatment were controlled by the use of the Nichols-Hough strain of organisms and by the use of a standard lot of arsphenamine, the minimal sterilizing dose of which over more than ten years had been 14 mg per kilogram of body weight. Thirteen of 51 rabbits infected with the treatment-resistant strain were not sterilized by injection of from 14 to 30 mg per kilogram of body weight. This refractoriness to treatment was sporadic, more pronounced in the beginning of the study, and less frequent as the strain became adapted to the new host. The study indicates that there is no regularity in the occurrence of refractoriness to treatment in rabbit syphilis, despite suggestive chains of instances of such resistance.

#### EXPERIMENTAL SYPHILIS

*Syphilitic Women as Passive Carriers*—As a factor in the spread of syphilitic infection, the sexually promiscuous woman with latent or treated syphilis long has been considered to play an important role as a passive carrier. Pariser<sup>12</sup> has subjected this preconceived belief to experimental study.

In his three experiments, *S. pallida* was introduced into the vaginas of women with early syphilis. Subsequently, a search for the organism was made by dark field microscopic examination and by inoculation of rabbits intratesticularly. Spirochetes thus introduced into the human vagina survived only a relatively short time. In one instance organisms were recognizable morphologically in the vagina until four hours after they were introduced, and in another they disappeared within one and a half hours, after which time the infectiousness of the vaginal secretions could not be demonstrated by animal inoculation.

*Infectiousness of Seminal Fluid*—In a study of the infectiousness of the semen of men with early syphilis, Pariser<sup>13</sup> found that seminal fluid did not transmit the disease to susceptible animals except when it was contaminated with *S. pallida* while passing over an open lesion containing the organisms. In his study, 23 specimens of seminal fluid from 20 men with early syphilis were used. Two experimental methods were employed. Ten specimens of seminal fluid were injected into the dorsal skin of mice, the peripheral lymph nodes, the spleen and in some instances the brain were removed twenty-one to forty days later, the macerated organs were suspended in saline solution and injected intratesticularly into rabbits. The remaining 13 specimens were injected directly into the testes of rabbits. Dark field examinations were made on all freshly passed seminal fluid specimens, but no spirochetes

12 Pariser, H. Studies of the Transmissibility of Syphilis. The Role of the Syphilitic Woman as a Passive Carrier, *J. Invest. Dermat.* 5:243 (Oct.) 1942.

13 Pariser, H. Studies of the Transmissibility of Syphilis. The Infectiousness of the Seminal Fluid of Men with Early Syphilis, *J. Invest. Dermat.* 5:311 (Dec.) 1942.

were seen in any of the specimens. The results of animal inoculation were also negative, except in 1 case in which the patient had moist papular lesions near the meatus and extending into the canal.

The author postulates that the male can transmit syphilis only during the presence of open lesions containing *S. pallida*, whether chronologically early or late in the course of the infection.

*Time Factor in Evaluation of "Cure" of Rabbit Syphilis*—The finding that the lymph nodes of untreated syphilitic rabbits remain infectious for years often in the absence of other demonstrable evidence of syphilis, has led many investigators to depend on the results of lymph node transfers as the ultimate criterion of cure in the experimental disease.

Eagle, Hogan and Kemp<sup>14</sup> enjoin caution in the interpretation of such negative lymph node transfers. They have found the time at which the transfer is made to be an important factor. Of 546 syphilitic rabbits treated with various arsenical drugs in doses approximately 25 to 75 per cent of the amount judged to be curative, 394 apparently were "cured" as judged by negative lymph node transfers into normal rabbits *six weeks* after treatment. However, when 279 of these "cured" animals were retested by a second node transfer *six months* after treatment, no less than 10 (37 per cent) were found still to harbor the organisms. The authors interpret these negative lymph node transfers followed by positive transfers as analogous to early infectious relapse in man.

Existing data as to the curative dosage of various antisyphilitic drugs must be reconsidered with attention to the time at which node transfers were made. Until that factor is rigidly controlled, temporary "cures" constitute a variable and indeterminable error which may vitiate the significance of much experimental data.

*Criteria of "Cure" of Rabbit Syphilis*—The evaluation of chemotherapeutic preparations depends on their effectiveness in ridding experimental animals of the invading organisms. It is difficult to be sure that an animal has been sterilized of spirochetes, and the criteria of "cure" are not universally agreed on.

Worms,<sup>15</sup> in a review of the subject, points out that, although recent workers appear to accept the validity of lymph node transfer as a safe procedure for the evaluation of antisyphilitic drugs, there is experimental evidence to indicate that success with this procedure is not entirely acceptable as a criterion of cure. This evidence is (1) the occurrence of "nullers," animals which acquire symptomless infection when inoculated with lymph node suspensions, (2) variability in the dissemination of the organisms throughout the organs of the body. Factors involved include the stage of the infection at which treatment is started and the interval of time between treatment and test of cure.

In testing the effectiveness of a chemotherapeutic preparation Worms suggests

(1) The preparation under examination should be tried finally not only on syphilitic rabbits but also on syphilitic mice. In rabbits it should be tried in the latent stage after the first outbreak of active symptoms, i. e., about three to four months after infection, and in mice not less than two months after the inoculation, when the infection of the central nervous system has been well established.

(2) The test by tissue transfer should be performed in rabbits not less than one year after the treatment, and during the year the rabbits should be closely watched for any signs of recurrence. In mice the test should be made in not less than six to eight months after treatment.

14 Eagle, H., Hogan, R. B., and Kemp, J. E. The Importance of the Time Factor in the Evaluation of "Cure" in Syphilitic Rabbits, *Am J Syph, Gonorr & Ven Dis* 26:557 (Sept.) 1942.

15 Worms, W. Evidence of Cure in Experimental Syphilis When Used for the Evaluation of Chemotherapeutic Preparations, *Brit J Ven Dis* 19:15 (March) 1943.

(3) For the transfer the material should be used as follows (a) Emulsions of a mixture of spleen, liver, marrow of several bones and testes of the treated rabbits, (b) emulsion of several lymph glands of the treated rabbit, (c) emulsion of whole organs (including brain, which should be transferred separately) and of several lymph glands of the treated mouse

Rabbit tissue emulsions should be inoculated into other animals, and if no signs of infection become apparent a second passage should be made To quote Worms further

Admittedly this is all troublesome but it is only by such thoroughness in testing that the inherent fallacies in the transfer method can be minimized, the trouble, time and expense are justified when a judgment of the value of a chemotherapeutic preparation depends on the result

*Experimental Primary Atrophy of the Optic Nerve*—Longley, Clausen and Tatum<sup>16</sup> have experimentally produced primary atrophy of the optic nerve in monkeys by the administration of various pentavalent arsenical compounds, including sodium arsinate, tryparsamide, acetarsone, 3-amino-4-beta-hydroxyethoxyphenylarsonic acid and 4- $\beta$ -( $\beta'$ -hydroxy)-ethoxyethoxyphenylarsonic acid The "approximate blinding dose" of acetarsone was found to be about three times, and of tryparsamide nearly nine times, that of sodium arsinate Of interest is the fact that 4- $\beta$ -( $\beta'$ -hydroxy)-ethoxyethoxyphenylarsonic acid, a compound which contains no amino group, produced characteristic visual damage in one of three animals tested The toxicity of the drug thus appears to be a function neither of the position of a nitrogen-containing side chain nor of its presence

This work makes available an experimental basis for study of the toxicity (blinding potentialities) of arsenical compounds and for evaluation of the prophylactic procedures designed to reduce or eliminate toxic optic neuropathy resulting from chemotherapy of syphilis of the central nervous system

McDermott and his co-workers<sup>17</sup> point out that the mechanism of the production of tryparsamide amblyopia has always been obscure They review the literature pertaining to the development of amblyopia following vitamin deficiency The B complex and vitamin A have both been incriminated It is difficult to determine the exact dietary factor concerned in the various clinical observations, since the deficiency is almost always a multiple one Likewise, the results in experimental animals are also not free from conflict, but it has been established that proper utilization of at least two dietary factors is necessary for the maintenance of the integrity of the nervous system in animals These two essential substances are vitamin A and some fraction or fractions of the B complex which is not thiamine, riboflavin or nicotinic acid

In the present experiment, young growing rats of both sexes were put on diets deficient in vitamin A and the B complex The authors summarize the experiment as follows

1 Deficiencies of vitamin A and of several components of the B complex were produced in rats Certain groups of these deficient animals as well as normal rats were treated with tryparsamide

2 Rats maintained on synthetic diets lacking only the complete vitamin B complex showed degeneration of the optic nerve This degeneration was intensified by the concurrent administration of tryparsamide

16 Longley, B J, Clausen, N M, and Tatum, A L The Experimental Production of Primary Optic Atrophy in Monkeys by Administration of Organic Arsenical Compounds, *J Pharmacol & Exper Therap* **76** 202 (Nov) 1942

17 McDermott, W, Webster, B, Baker, R, Lockhart, J, and Tompsett, R Nutritional Degeneration of the Optic Nerve in Rats Its Relation to Tryparsamide Amblyopia, *J Pharmacol & Exper Therap* **77** 24 (Jan) 1943

3 Rats maintained on the same synthetic diet supplemented either with brewer's yeast or with all the available crystalline B-vitamins together (thiamine hydrochloride, riboflavin, nicotinic acid, pyridoxine, calcium pantothenate and choline chloride) showed no degeneration of the optic nerve, whether or not they had received tryparsamide

4 Rats maintained on diets which were partially deficient in pantothenic acid failed to show any degeneration of the optic nerves, whether or not they had received tryparsamide

5 The deficiency responsible for the nerve degeneration in completely B-deficient rats is attributable to one or more of the known crystalline members of the group. It is not pantothenic acid alone

6 Rats maintained on synthetic diets completely free of vitamin A developed marked degeneration of the optic nerves

7 There was no evidence that the administration of tryparsamide intensified this process. The changes in the tryparsamide treated animals were, if anything, somewhat less than in the untreated animals, but this effect is probably only an apparent one as the changes were extensive in both groups

8 Rats maintained on diets poor in vitamin A which were treated with tryparsamide, showed degenerative changes in the optic nerves although they showed no clinical signs of A deficiency

9 The degenerative changes in the low vitamin A group were of much less extent than in the completely deficient animals, either treated or untreated

10 Rats maintained on synthetic diets supplemented by adequate amounts of B-complex (yeast) and vitamin A (cod liver oil) developed no degeneration of the optic nerve, whether or not they were treated with tryparsamide

#### SYPHILOID DISEASES

*Pinta*—An extensive review of the literature relating to pinta has been made by Holcomb,<sup>18</sup> who cites 177 references. Pinta has been reported in the southern states of Mexico, Colombia, Venezuela, Brazil, Ecuador, Peru and the West Indies, where it affects principally Negroes, native Indians and peoples of mixed blood. Descriptions of the disease are not limited to the Western Hemisphere, however, for cases have occurred on the east and west coasts of Africa, in Egypt, Tunisia, Algeria, Morocco and Iraq, and among the dark-skinned races in India, Straits Settlement and the Philippine Islands.

The etiologic agent, a spirochete morphologically indistinguishable from *S. pallida* and *Treponema pertenue*, was first identified by two Cuban physicians, Grau Triana and Alfonso Amenteros. It has been named variously *Treponema carateum*, *Treponema herrejoni*, *Treponema pictor*, *Treponema americana*, *Treponema discromoderma*, and *Treponema pinta*. A limited number of inoculations into guinea pigs, rabbits and rats have given negative results. Serologic tests for syphilis are usually positive, especially after the disease becomes chronic.

Several insects have been found to harbor the spirochete of pinta and are thought by some to be vectors of the disease. Others believe personal contact to be more important, pointing out that the organism can be demonstrated in the perspiration of infected persons.

In tracing the antiquity of literature on hyperpigmentation and depigmentation Holcomb discusses the question of whether pinta originated in the Western Hemisphere or was imported from Africa. He also indicates certain relationships to yaws and syphilis, concluding that "A review of the literature would seem to me to indicate that this syphiloid is one of the many disguised evidences of the antiquity of syphilis."

Beerman<sup>19</sup> defines pinta (mal del pinto, carate, azul) as

18 Holcomb, R. C. Pinta, A. *Treponematoses*, U. S. Nav. M. Bull. 40 517 (July) 1942

19 Beerman, H. Pinta—A Review of Recent Etiologic and Clinical Studies, *Am. J. M. Sc.* 205 611 (April) 1943

a chronic endemic disease of long duration, infectious, possibly contagious or transmissible by an as yet unknown vector. It is characterized by papular or papule-like initial lesions and is followed in a variable but usually long time by an erythematous eruption which increases continuously and is transformed into dermatitic plaques which are superficial, atrophic, pigmented and achromic, accompanied frequently by palmar or plantar keratodermias, and enlargement of superficial lymph nodes. It is now supposed to be due to a specific treponema. The cutaneous lesions are at times accompanied by visceral changes (aorta, nervous system).

Pinta affects dark-skinned peoples chiefly. It is essentially a disease of rural communities and is most prevalent in river valleys. Persons of the poorer classes, laborers and persons living under unsanitary conditions most often are affected. It occurs mostly between the ages of 10 and 20 years. The mode of transmission is thought to be direct contact, intimate and prolonged, but the possibility of an insect vector exists.

Serologic tests of the blood for syphilis, both complement fixation and flocculation, give uniformly high percentages of positive reactions, especially during the later stages of the disease. The treatment of pinta is similar to that of syphilis and of yaws. Seroresistance is the rule rather than the exception. As Beerman says

Pinta thus represents another milestone in the efforts to evaluate the syphilis-like diseases.

With the discovery of an organism, morphologically indistinguishable from *Spirochaeta pallida*, the laws of Koch have been fulfilled only a little less than in syphilis. But with this discovery of the treponemal cause of pinta, comes rationalization of effective therapy previously used empirically. With increased knowledge of the clinical aspects of the disease and the possible modes of its transmission, prophylaxis can be successfully employed. Credit is due to the indefatigable industry of the workers in our neighboring Latin American countries.

In Venezuela, according to Iriarte,<sup>20</sup> pinta is found mostly in the western states and in the extreme south. Studies purporting to establish a mycologic causation are considered untenable, since many of the fungi described are saprophytic on the skin of animals and man. *T. carateum*, while found readily in the dyschromic cutaneous lesions, has not been demonstrated in the lymph nodes of patients with pinta.

#### SERODIAGNOSIS OF SYPHILIS

*Spirochetal Antigens*—There is reason to believe that an antigen made from pure cultures of pathogenic *S. pallida* would be more specific than the tissue antigens now used in the serologic laboratory. The difficulty is, of course, in obtaining pure cultures or organisms which retain their pathogenicity.

Sordelli<sup>21</sup> summarized the various attempts which have been made to utilize spirochetal antigens in serodiagnosis. Although no original work is presented, this article provides a splendid summary of the subject. The relationship between reagin and immunity, the cross reactions between various strains of pathogenic and cultivated spirochetes and the results obtained with human serums with various spirochetal antigens are all described. To date, the hope that biologic false positive reactions can be excluded by using these antigens has not been realized. In yaws and pinta, results are similar to those obtained with tissue antigens, in malaria, positive reactions are common, but in leprosy the proportion of falsely positive reactions is less than with standard tests.

*Antigens Flagellar and Somatic*—The fact that antisera to somatic type antigens lose their flocculating power with less heating than do antisera to flagellar type antigens generally has been accepted as evidence that antibodies to

20 Iriarte, D. R. En carate en Venezuela, Rev. de med. trop. y parasitol., bacteriol., clin. y lab. 8:75 (Nov-Dec) 1942.

21 Sordelli, A. Las espiroquetas como antígeno, Rev. argent. dermatosif. 26:777, 1942.

the two kinds of antigen differ in their resistance to heat. Bawden and Kleczkowski<sup>22</sup> report experiments to show that this different reactivity to heat depends on the presence of albumin. If euglobulin fractions of antisera were prepared and heated separately, there was no difference in the amount of heating required to destroy the flocculating power of different antibodies. Only when the antibodies to the two types of antigen were heated in the presence of albumin was there any difference in their behavior. When ability to fix complement or to neutralize infectivity was used as a criterion of the presence of residual antibodies, instead of ability to cause flocculation, all antisera were found to be equally susceptible to heat. The fact remains, however, that heating (to 75 C for ten minutes) destroys the ability of antiserum to somatic type antigens to cause flocculation although not its ability to combine with the antigens.

In view of the known differences, e. g., the thermolability of various antibodies attempts to differentiate true syphilitic reagin from nonspecific substances (antibodies?) of nonsyphilitic serums continue to offer some promise. Kahn's several "verification" tests represent efforts in this direction, even if their consistency and specificity are yet to be proved.

*Natural Tissue Antibody*—Kidd and Friedewald<sup>23</sup> described experiments which demonstrate the presence of a natural antibody in the blood of normal adult rabbits which reacts in vitro with a sedimentable constituent of normal rabbit tissue cells. The substance with which the natural tissue antibody reacts is regularly present in saline extracts of many normal tissues. The titer of this principle was found to run parallel with that of two natural antibodies also present in normal rabbit's blood (natural Wassermann reagin and natural anti-sheep hemolysin), but absorption tests showed it to be distinct from these.

The natural tissue antibody apparently fails to react in vivo with normal tissue substance. In this respect, it is comparable to Wassermann reagin, since although the tissues of syphilitic patients contain antigenic substances and antibody to this substance is present in the blood serum, no demonstrable reaction occurs in vivo.

*Zone Reactions*—As with other serologic procedures, such as the Widal test for typhoid, so also with serologic tests for syphilis there is occasionally observed a prezone phenomenon responsible for false negative reactions of serums which should give a strongly positive reaction. With such serums it is necessary to test serial dilutions to bring out the positive reaction.

Myers and Perry,<sup>24</sup> testing serums from 2,052 patients whose reactions to routine flocculation tests (Kline exclusion) were negative, found 6 showing the prezone phenomenon. In addition to those specimens which gave a negative reaction to the original flocculation test, there were 29 other specimens with atypical doubtful reactions which were really prezone positive reactions. The authors also comment on "an anomalous zone reaction in sera from presumably nonsyphilitic individuals" which they observed 84 times in their study. Unfortunately the clinical status of these patients was not determined. Myers and Perry consider it advisable to use two tests on each specimen of serum, and when it is

22 Bawden, F. C., and Kleczkowski, A. The Antigenicity of Non-Precipitating Complexes. *Brit J Exper Path* **23** 169 (Aug) 1942, The Effects of Heat on the Serologic Reactions of Antisera, *ibid* **23** 178 (Aug) 1942.

23 Kidd, J. G., and Friedewald, W. F. A Natural Antibody That Reacts in Vitro with a Sedimentable Constituent of Normal Tissue Cells. I. Demonstration of the Phenomenon. II. Specificity of the Phenomenon, General Discussion, *J Exper Med* **76** 543 (Dec) 1942.

24 Myers, R. M., and Perry, C. A. The Occurrence of Zone Reactions in Flocculation Tests for Syphilis, *Am J Syph, Gonorr & Ven Dis* **26** 494 (July) 1942.

not feasible to perform more than one test they recommend that at least two different quantities of serum be used routinely

*Antibody Formation and the Anamnestic Reaction*—In a review of the general problem of antibody production and the anamnestic reaction (the phenomenon of antibody "recall" under the stimulus of specific and nonspecific antigens), Cannon<sup>25</sup> states

The anamnestic reaction may play a beneficial role in the treatment of chronic or focal infections in which, presumably, foci of infective agents persist in the tissues over long periods of time. For example, in the treatment of chronic syphilis, arthritis, or iritis, stimulation of the antibody mechanism by various foreign protein materials, such as typhoid vaccine, milk, malarial parasites, or by hyperthermic means may cause the liberation into the blood stream of significant amounts of specific antibodies engendered by previous antigenic experiences but which could not otherwise gain access to the infected foci.

The facts suggest that antigenic components may persist within antibody-producing cells for considerable periods of time after infection or vaccination and thus are able to function as 'templates' when later stimuli cause an acceleration of antibody production.

Whenever (antibody) is formed, antigenic 'templates' may so influence the structural pattern of the globulin molecules as to confer specific properties upon them. Some of these molecules may pass into the extracellular fluids as antibodies and remain there for variable periods of time, others may persist within their cells of formation. The persistence of this antibody matrix for months or years may explain both the acquisition of acquired resistance independently of any considerable amounts of antibodies in the blood as well as many of the tissue reactivities which are commonly regarded as allergic phenomena.

*Absence of Reagin from Urine*—Shortly after the discovery of complement fixation and its application to the serodiagnosis of syphilis, several investigators reported the presence of a complement-fixing substance in the urine of patients with syphilis. Other workers, finding urine anticomplementary, were unable to confirm this finding.

Scott,<sup>26</sup> who has tested the urine of 23 patients with syphilis and of 8 non-syphilitic controls, reports that in no instance was reagin demonstrable by complement fixation. Five patients with syphilis had albuminuria, 1, a patient with early syphilitic nephrosis, excreting 2.0 Gm of albumin per liter. None of the specimens of urine, however, contained reagin, despite the fact that the blood reagin titers ranged between 24 and 48 units. Urine frequently was found to be anticomplementary despite neutralization. This anticomplementary activity seemed directly proportional to the volume of urine.

The author concedes that an occasional patient may excrete reagin in the urine. For this to occur, two factors appear necessary: first, a relatively high percentage of globulin in the excreted protein, which presupposes severe damage to the glomerular filter; second, a high reagin content in the blood serum. Neither of these factors existed in sufficient degree in the patients of the group here studied.

*Weltman's Serum Coagulation Reaction in Syphilis*—When normal human serum is diluted 1:50 with differently concentrated solutions of calcium chloride in distilled water, different intensities of turbidity and flocculation occur after fifteen minutes of heating. In certain diseases the serum coagulation becomes altered, and it has been claimed that by determining the concentration "band" at which coagulation occurs it is possible to differentiate "exudative" from "fibrotic" conditions.

25 Cannon, P. R. Antibody Production and the Anamnestic Reaction, *J. Lab. & Clin. Med.* 28:127 (Nov.) 1942.

26 Scott, V. Note on Absence of Syphilitic Reagin and Antigenic Substance in Urine, *Bull. Johns Hopkins Hosp.* 71:242 (Oct.) 1942.



Steiner,<sup>27</sup> who has studied the serum coagulation reaction in a group of 72 syphilitic patients, reports that in general the coagulation bands tended toward moderate but distinct prolongation, although in most instances they were not specific alterations. No distinct differentiation among the various stages or manifestations of syphilis was possible. No relation was present between the coagulation reaction and the Wassermann reaction.

*Colloidal Gold Reaction*—It has been impossible heretofore to study the effects of the individual globulin fractions on colloidal gold precipitation, because these fractions could not be obtained in pure form. Gray,<sup>28</sup> using pure protein fractions prepared electrophoretically, has studied the effects on the colloidal gold flocculation of pure human albumin, gamma globulin and the fraction containing alpha and beta globulins.

The addition of pure gamma globulin to normal spinal fluid produced a dementia paralytica type colloidal gold curve. The degree of flocculation was proportional to the amount of gamma globulin added. Similar concentrations of the fraction containing alpha and beta globulin did not affect the colloidal flocculation. The addition of pure human albumin to cerebrospinal fluid of a patient with dementia paralytica converted the curve to normal. Since the gamma globulin is increased in the spinal fluid of patients with dementia paralytica, the colloidal curve typical of that disease probably depends on the relative increase in gamma globulin.

Studying the protein components of cerebrospinal fluid with the Tiselius electrophoresis cell, Kabat, Moore and Landow<sup>29</sup> found that the electrophoretic pattern of spinal fluid resembles that of serum and that alterations in the composition of the serum proteins are reflected in the spinal fluid. In neurosyphilis, an increased gamma globulin occurred in the cerebrospinal fluid. No such change was found in the blood serum. This suggests that not all of the spinal fluid protein is derived from the blood, since it is difficult to imagine an altered permeability of the hematoencephalic barrier which could produce an increase in gamma globulin without producing an increase in the smaller albumin molecule.

Colloidal gold activity of the cerebrospinal fluid was found to be associated with increases in the gamma globulin fraction, whereas albumin appeared to inhibit this reaction.

#### FALSE POSITIVE REACTIONS TO SEROLOGIC TESTS

Summarizing the present status of biologic false positive serologic reactions for syphilis, Eagle<sup>30</sup> outlines the procedures which have been suggested for differentiating syphilitic reactions from those due to other conditions.

Two of the suggested procedures are the differential temperature "verification" test of Kahn, which "is not yet a test on which to base a definite opinion as to the significance of a positive result," and the spirochetal complement fixation test, the results of which are "so completely at variance that it is well to withhold judgment." To quote further:

Fundamental studies on the nature of the substance responsible for these biologic false reactions are clearly indicated. At the onset, it may be advisable to distinguish between four

27 Steiner, K. Weltman's Serum Coagulation Reaction in Cases of Dermatoses and of Syphilis, *Arch Dermat & Syph* 46 87 (July) 1942

28 Gray, S. J. Studies on the Mechanism of the Spinal Fluid Colloidal Gold Reaction, *Proc Soc Exper Biol & Med* 51 401 (Dec) 1942

29 Kabat, E. A., Moore, D. H., and Landow, H. An Electrophoretic Study of the Protein Components in Cerebrospinal Fluid and Their Relationship to the Serum Proteins, *J Clin Investigation* 21 571 (Sept) 1942

30 Eagle, H. Biologic False Positive Serologic Tests for Syphilis, editorial, *Am J Syph, Gonorr & Ven Dis* 26 641 (Sept) 1942



types of reagin, some of which may ultimately prove to be identical (a) The flocculating factor present in minute traces in many normal human sera, (b) the 'reagin' present in the occasional human serum in amounts sufficient to give positive or doubtful diagnostic tests, (c) the 'reagin' elaborated in the course of such nonsyphilitic diseases as leprosy, malaria, cowpox, and infectious mononucleosis, to mention only a few, and finally, (d) the 'reagin' elaborated in the course of syphilitic infection

Corollary to the possible chemical identification of the serum components responsible for the several types of reactivity, studies should be carried out on the fractionation of crude tissue extracts used as 'antigen' in the Wassermann and flocculation tests, for it is possible that the different types of 'reagin' react with different substances in those extracts

*False Positive Reactions Following Routine Immunizations*—Alterations in the blood serum brought about by routine United States Army immunizing procedures against various diseases (smallpox, typhoid, yellow fever and tetanus) have been shown by Arthur and Hale<sup>31</sup> to influence the results of the Kahn flocculation test for syphilis. Serologic tests were performed on 94 recruits who had received routine Army preventive inoculations. Of those studied, 14 (14.8 per cent) were found to have temporarily positive Kahn reactions. This change persisted for one or two months and then disappeared. It is not possible to determine from the data given whether the falsely positive serologic reactions resulted from any one of the inoculations or from the combination of all four.

Because of the extensive use of serologic tests for syphilis among military service personnel who may have received preventive inoculations shortly before the observation that temporarily falsely positive reactions for syphilis may result from these inoculations is a timely contribution to the serodiagnosis of syphilis.

*False Positive Reactions Following Smallpox Vaccination*—Favorite<sup>2</sup> has confirmed the observation that smallpox vaccination may cause a falsely positive serologic reaction for syphilis. A group of 202 medical students and nurses known to have negative serologic reactions were vaccinated and repeatedly tested with Kolmer, Kahn and Mazzini tests. Twenty-four persons (11.8 per cent) had positive reactions at one time or another following the vaccination. The patients with positive reactions were retested every two weeks. There was a gradual diminution in the intensity of the reactions until all became negative by the end of one hundred and twenty days.

Lubitz<sup>32</sup> considers smallpox vaccination an important cause of biologic false positive serologic reactions for syphilis. He has performed serologic tests on 100 persons whose vaccination resulted in primary "takes." Of these, 13 gave positive reactions. There was no consistent evidence of heterophile antibody formation, and the Kahn verification test gave no conclusive indication that these were false positive reactions.

*Specificity of Serologic Reactions During Pregnancy*—In the earlier literature on serodiagnosis, the belief frequently was expressed that during pregnancy serologic tests for syphilis were unreliable. That this belief is entirely false is again substantiated by the data of Kandler<sup>31</sup>. Several different techniques were used in the study of 10,354 pregnant women, and no evidence was found that either the sensitivity or the specificity of the serologic procedures was impaired.

31 Arthur, R. D., and Hale, J. M. Biologic False Positive Tests for Syphilis Associated with Routine Army Immunizations, *Mil Surgeon* **92** 53 (Jan) 1943

32 Favorite, G. O. Effects of Smallpox Vaccination (Vaccinia) on Serologic Tests for Syphilis, *Proc Soc Exper Biol & Med* **54** 297 (April) 1943

33 Lubitz, J. M. Serologic Reactions Following Smallpox Vaccination, *Proc Inst Med Chicago* **14** 343 (Feb) 1943

34 Kandler, H. Ueber die Zuverlässigkeit der Seroreaktionen auf Syphilis bei Reihenuntersuchungen von Schwangeren, *Arch f Dermat u Syph* **181** 315, 1940

*False Positive Reactions in Infants and Children*—Surveying the results of approximately 26,700 flocculation tests for syphilis made in pediatric service, Hill <sup>35</sup> found 114 tests made on 37 patients which elicited proved false positive or false doubtful reactions. A major portion of the nonspecific reactions noted in the study occurred in patients with infections of the respiratory tract in particular and acute infections in general, but occasional false doubtful and false positive reactions occurred with a variety of other conditions.

*Serologic Reaction Approaching "Universal Sensitivity"*—Kahn and his co-workers <sup>36</sup> have studied the extent to which it is possible to increase the number of false positive reactions given by a serodiagnostic test by increasing the sensitivity of the test. The use of excessively sensitive antigens gave as high as 40 per cent false positive reactions. The use of such antigens with the test performed at 1 C resulted in about 80 per cent false positive reactions. When, in addition, unheated serums were used (rather than serums heated for thirty minutes at 56 C), the nonspecific sensitivity approached 100 per cent. These findings suggest to the authors the existence of a universal serologic reaction which may afford the basis for false positive reactions obtained with serodiagnostic tests.

*"Verification" Tests*—A new method purporting to "verify" the results of questionable serologic tests for syphilis is described by Kahn <sup>37</sup>. This new procedure is based on the effect of different concentrations of electrolytes on the flocculation reaction.

A higher titer on serial dilution with 2.5 per cent solution of sodium chloride than with 0.9 per cent concentration denotes, according to the author, a "syphilitic type" of reaction, whereas a higher titer on serial dilution with 0.9 per cent salt solution than with 2.5 per cent concentration denotes a "general biologic (non-syphilitic) type" of reaction.

This new "verification" procedure has not yet been applied to any large series of cases, and its ultimate place in the serodiagnosis of syphilis, therefore, awaits further study. Its precursor, based on variations in reactivity at different temperatures, has not been widely accepted.

Carter <sup>38</sup> believes the differential temperature "verification" test procedure can be improved by the use of parallel quantitative reactions run at temperatures 37 and 1 C, thus furnishing a contrasting relationship of the strength of the reactions of a serum at the two temperatures.

Briceño Rossi <sup>39</sup> has attempted to distinguish serum reagin due to syphilis from that due to yaws and pinta by using Kahn's differential temperature "verification" test. In general, the serums of patients with yaws or pinta gave the "syphilitic" type of reaction rather than the "general biologic" type. Serums from 30 lepers were also tested. 19 gave negative reactions, 4 gave equally positive reactions at 37 and at 1 C, 3 gave the "syphilitic" type reaction and 4 the "general biologic" type.

35 Hill, A. Nonspecific Serologic Reactions for Syphilis in Infants and Children, *J Pediat* **21** 207 (Aug) 1942.

36 Kahn, R. L., Marcus, S., McDermott, E. B., and Adler, J. Serologic (Nonsyphilitic) Reaction Approaching Universal Sensitivity, *J Invest Dermat* **5** 459 (Dec) 1942.

37 Kahn, R. A New Verification Method in Serology of Syphilis. A Preliminary Report, *Univ Hosp Bull, Ann Arbor* **8** 45 (June) 1942.

38 Carter, B. B. The Use of a Quantitative Test in Verification Procedures, *Am J Syph, Gonorr & Ven Dis* **26** 629 (Sept) 1942.

39 Briceño Rossi, A. L. El valor del verifications test, en la serologia del carate o mal del pinto y buba (pian o yaw), *Rev san y asist Soc* **8** 153 (Feb) 1943.

*False Negative Serologic Reactions*—Many recent publications have stressed the importance of false positive serologic reactions for syphilis. Souders<sup>40</sup> properly notes that there may be false negative reactions as well. Serum from a syphilitic patient with active manifestations of the disease may give a negative reaction from laboratory error, because of low sensitivity of the test used, when the infection had existed for many years and if therapy had been employed. Other causes not mentioned by Souders include the occurrence of a zone phenomenon and the occasional finding of a person whose response to syphilitic infection does not include the elaboration of reagin.

#### PREVALENCE OF SYPHILIS

*The Problem of Measurement*—Inherent in any program to control syphilis is the problem of measuring the frequency of the disease and its trend in relation to that program over a period of years. Attempts at measurement in the past have not been generally satisfactory, either because the data on which they were based were not reliable or because the significance of those data was not properly interpreted.

Turner<sup>41</sup> discusses some of the underlying principles of the measurement of syphilis. He points out that in the measurement of the frequency of the disease, data related to *incidence* (the rate at which persons are being infected) must be differentiated from data related to *prevalence* (the accumulation of affected persons in the community).

Factors other than the actual frequency of syphilis may cause variations in the crude incidence and prevalence rates. Moreover, changes in the group under study may result in variations in the frequency of syphilis quite independent of the operation of control measures. Unless correction is made for these variables, data for one year may not be comparable with those of another. The principal variable factors are those related to the individual patient (variable criteria for the diagnosis of syphilis, variation in sensitivity and specificity of serologic tests) and those related to the group being studied (race, sex, age, social and economic factors, selection of patients included in the study group).

The author reviews recent studies on the incidence and prevalence of syphilis in the United States, concluding that most are so weighted with selective factors of one sort or another that direct comparisons from year to year to determine the trend of the disease cannot be made.

*Discovery Rates*—Each year in a given community a certain number of cases of syphilis are discovered medically for the first time. When the number of these newly discovered cases is related to the population of the community, discovery rates may be derived, and these rates may be used as one index of the trend of the disease within the community.

A discussion of the reliability and significance of such discovery rates obtained from the study of an urban area over a nine year period from 1932 to 1940 inclusive has been given by Turner and his co-workers.<sup>42</sup>

In the Eastern Health District of Baltimore, the mean annual discovery rate for all cases among Negroes was 26.7 per thousand of population and among white

40 Souders, C. R. The Importance of False Negative Blood Tests for Syphilis, *Lahey Clin Bull* **3** 27 (July) 1942.

41 Turner, T. B. Studies on Syphilis in the Eastern Health District of Baltimore City I Principles Concerned in Measuring the Frequency of the Disease, *Am J Hyg* **37** 259 (May) 1943.

42 Turner, T. B., Dyar, R., Clark, E. G., and Birkhead, M. F. Studies on Syphilis in the Eastern Health District of Baltimore City II Discovery Rates as an Index of Trend, *Am J Hyg* **37** 273 (May) 1943.

persons 1.41 per thousand. Among white persons the mean age-specific discovery rate was highest for the age group 25 to 34 years. Among the Negroes the highest rate was in the 20 to 24 year group. Among both racial groups, the age-specific discovery rates for females were higher than those for males in the younger age group and lower after 25 years. For all ages, the rate for white females was slightly lower than that for males, but among Negroes, there was not any significant difference between the total rates for males and females. In general, Negroes tended to be infected at an earlier age than white persons, and the females of each race tended to be infected at an earlier age than the males.

With regard to the trend of syphilis in the district, the following conclusions are drawn: (1) A substantial reduction in the occurrence of congenital syphilis was noted during the study period, (2) among white persons a significant decline in the mean annual discovery rate occurred, (3) among Negroes there was no convincing evidence of a downward trend in the disease. Discovery rates for total cases of syphilis and discovery rates for cases of early stages showed an upward trend.

*Frequency of Syphilitic Lesions at Autopsy*—A significant contribution to the knowledge of the prevalence and the ultimate outcome of syphilitic infection has been made by Rosahn and Black-Schaffer, who have made an extensive and well planned study to correlate clinical and postmortem observations on 5,300 patients at the New Haven Hospital.

Their first paper,<sup>43</sup> as yet unpublished but summarized in their second, is devoted to a review of the literature on the frequency of the changes attributed to acquired syphilis in autopsies on persons over 20 years of age. It was found that changes attributed to syphilis observed at autopsy by 17 investigators varied from a low incidence of 2.6 per cent to a high of 29.5 per cent, with a combined average of 5.45 per cent among 146,761 adults. Analyzing the discrepancies between the findings of different investigators, the authors conclude that the differences are largely based on variability in the histologic changes considered to be evidences of syphilis.

For their own data, Black-Schaffer and Rosahn<sup>44</sup> reviewed 5,300 postmortem examinations performed at the Yale University School of Medicine, of which 3,907 were on patients aged 20 years or more. Three hundred and eighty of the 3,907 patients (9.7 per cent) had clinical, laboratory or postmortem evidence of syphilis. The punch card code used in the study is described in detail. In their third paper, Rosahn and Black-Schaffer<sup>45</sup> discuss the prevalence of the anatomic changes produced by syphilis in adults. In the group of 380 syphilitic patients were 156 persons with morphologic lesions of syphilis. Of the 224 remaining patients, without lesions at autopsy, about half had never received treatment, and a majority had had the diagnosis made by serologic tests alone. Ninety of the 156 patients with anatomic lesions died primarily as a result of syphilis. In the authors' experience, 3 out of 10 persons with syphilis diagnosed by clinical methods had significant lesions in the tissues, and 1 out of 5 died therefrom.

Syphilitic lesions were from two to four times as frequent in Negroes as in white persons. Nevertheless, the syphilitic Negroes appeared no more likely to

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43 Rosahn, P. D., and Black-Schaffer, B. Studies in Syphilis. I. Review of the Incidence of Syphilis in Autopsies on Adults, *Arch. Int. Med.* **72**: 78, 1943.

44 Black-Schaffer, B., and Rosahn, P. D. Studies in Syphilis. II. Methods of Analysis of Yale Autopsy Protocols, Including a Code for the Punched Card Study of Syphilis, *Yale J. Biol. & Med.* **15**: 575 (March) 1943.

45 Rosahn, P. D., and Black-Schaffer, B. Studies in Syphilis. III. Mortality and Morbidity Findings in the Yale Autopsy Series, *Yale J. Biol. & Med.* **15**: 587 (March) 1943.

have demonstrable lesions and had no greater chance of dying from the disease than the white patients. The mean age at death of syphilitic and of nonsyphilitic Negroes was identical, but both of these two groups died at a significantly earlier mean age than white persons of comparable categories. This observation suggests that the shorter life expectancy of Negroes as contrasted to white persons may be due not to the greater frequency of syphilis among Negroes but rather to non-specific social and economic influences which adversely affect their life span.

Sex appeared to have an influence on resistance to the tissue changes of late syphilis, since syphilitic males with lesions at autopsy constituted 47 per cent of the male population, whereas syphilitic females with lesions were only 27 per cent of the female population, and 44 per cent of the males had demonstrable lesions, in contrast to 33 per cent of the females.

In white patients, the mere fact of syphilitic infection appeared significantly to reduce longevity, regardless of whether or not tissue lesions resulted.

*Prevalence of Syphilis in Selectees*—The Selective Training and Service Act of 1940 requires a routine serologic test for syphilis as part of the general examination of every draftee and volunteer. Copies of the reports are forwarded to the United States Public Health Service. An analysis of 1,895,778 such reports on men of draft age has been made by Vonderlehr and Usilton.<sup>16</sup>

The rate of prevalence of syphilis (based on positive and doubtful reactions to serologic tests) among the selectees examined is 45.3 per thousand. Among Negro selectees, the rate of prevalence is 252.3 per thousand, and among white selectees, 17.4 per thousand. In those localities where rates among Negroes are highest, the rates for white persons are relatively higher than in areas where the rates among Negroes are low.

Analyzed geographically, the highest prevalence rates are found in the Southeastern states, the lowest, in the New England, West North Central and Middle Atlantic states. Among selectees from rural areas, the rate of syphilis prevalence is 43.8 per thousand, for those from urban communities, a somewhat higher rate, 46.1 per thousand, is recorded.

As might be expected, syphilis is more prevalent in the older age groups. For example, white urban dwellers had a rate almost four times higher in the age group 31 to 35 years than in the age group 21 to 25 years. This, of course, does not mean that older men more frequently are exposed to syphilitic infection, but indicates rather that there is an accumulation of unrecognized infections in the older age groups.

The information gained from the routine serologic testing of draftees is of great interest to the epidemiologist, and of practical value in determining where venereal disease control activities should be concentrated. The analysis of these serologic tests is indeed the most accurate information available as to the prevalence of syphilis in this country.

*Prevalence of Syphilis Among Negroes*—As Smilie<sup>17</sup> points out, the most extraordinary fact brought out by analysis of the results of serologic tests on selectees is the high prevalence of syphilis in the Negro. In all parts of the United States the rate in Negro men is at least ten times higher than in white men.

The geographic distribution of the disease bears a direct relationship to the distribution of the Negro population of the nation. States with a large population of

46 Vonderlehr, R. A., and Usilton, L. J. Syphilis Among Men of Draft Age in the United States, *J. A. M. A.* **120** 1369 (Dec. 26) 1942.

47 Smilie, W. G. Syphilis in the United States Primarily a Negro Problem, *J. A. M. A.* **122** 365 (June 5) 1943.

Negroes have the highest syphilis rates. Furthermore, those states having highest syphilis rates in Negroes concomitantly have a higher than average syphilis rate in white men. Thus, the major syphilis problem in the United States at the present time centers in the high prevalence of the disease in the Negro.

Comparisons of syphilis prevalence in the United States and in other nations are not valid unless the data presented are truly comparable. When so interpreted, it becomes clear, says Smillie, that in the white population of the United States there is a syphilis rate that compares favorably with that of any nation in the world.

From the point of view of the public health administrator, the issue is cleancut, he must attack the disease most vigorously where it is most prevalent. Since syphilis is more than ten times as prevalent in Negroes as in white persons, ten times as much emphasis should be placed on control of the disease in the Negro race.

Brumfield, Lade and Feldman<sup>48</sup> discuss the prevalence and trend of syphilis in New York state (exclusive of New York city) based on five years' experience with improved morbidity reports. Over the entire period, 79,991 cases of syphilis were reported, of which 71,001 (89 per cent) were classified as instances of acquired syphilis. Of these cases of acquired syphilis, in only 11 per cent was the disease stated to be in an early stage. Prevalence and attack rates were lower in the females than in the males, but the age distribution was essentially the same for the two sexes.

A progressive decline in the number of cases of early syphilis reported and in prevalence and incidence rates was observed during the five year period of study. The decrease was proportionately greater for younger persons, a significant finding, since in this group there is a preponderance of infectious lesions. Notable also is the observation that the decline was more pronounced in cities of 10,000 population and over, in which greater effort was made to control the disease.

*Actuarial Data*—Actuarial data which have been used as an index of prevalence of syphilis are by no means satisfactory. There is a tendency to conceal syphilis as a cause of death. Autopsy studies give no indication of the number of patients who have been "cured," whether spontaneously or as a result of antisyphilitic treatment.

In the years 1917 to 1940 inclusive, the adjusted death rate for syphilis for white policy holders of the Metropolitan Life Insurance Company<sup>49</sup> has shown an average annual decrease of 3.9 per cent and for Negro policy holders an increase of 0.5 per cent per year. The adjusted death rate in the first five years of this period was 14.0 per hundred thousand for white persons and 34.0 for Negroes, in the last five years, 7.0 and 37.3 respectively.

The reviewers cannot, however, refrain from commenting that existing actuarial information concerning syphilis is inaccurate, inadequate and incomplete. To estimate the hazard of death from "syphilis" by lumping together in a single group persons with early and latent syphilis, for whom the prognosis after adequate treatment is exceptionally good, and those with late lesions (especially cardiovascular and neurosyphilitic), for whom the prognosis after any sort of treatment may be exceptionally bad, to fail to consider the adequacy of treatment and to base actuarial opinion on serologic standards which are rapidly becoming obsolete and outmoded.

48 Brumfield, W. A., Lade, J. H., and Feldman, L. L. The Epidemiology of Syphilis Based upon Five Years Experience in an Intensive Program in New York State, *Am J Pub Health* 32:793 (Aug) 1942.

49 The problem of Syphilis, *Statist Bull Metrop Life Insur Co* 23:8 (Oct) 1942.

constitute thoroughly unsound actuarial as well as medical practice, and work a profound injustice on many applicants for life insurance. The entire subject of the actuarial hazard of syphilis is badly in need of review by a joint group of clinicians, serologists, pathologists, actuarial experts and independent statisticians.

*Syphilis Among Alien Seamen*—Among alien seamen examined at the New York Quarantine Station, reports Burow,<sup>50</sup> the discovery rate of syphilis began to rise toward the end of 1939, reached a peak in the fall of 1940 and has been maintained at a consistently high level since then, being roughly at three times the prewar level. Since May 1941, the discovery rate for gonorrhea has decreased, probably because of the increasingly large number of foreign vessels that carry and utilize sulfonamide compounds.

#### EPIDEMIOLOGY

A method of syphilis case finding which has received considerable emphasis in recent years is that of contact investigation, particularly as applied to cases of infectious early syphilis.

McIlhany and Smith<sup>51</sup> stress the importance of concentrating efforts at contact investigation on patients with early syphilis. The disease being more transmissible during the first year of infection, epidemiologic studies are most productive if confined to cases of primary and secondary and early latent syphilis of less than one year's duration.

Writing on the epidemiology of communicable venereal disease, Goodman<sup>52</sup> metaphorically compares contact investigation to individual sharpshooting, and screening procedures to spraying the skies with shot to bring down unmarked birds. The essential steps in contact investigation are listed as (1) *selection* of the patient to be interviewed, (2) *introduction* to determine the patient's identity, (3) *revelation* of contact information, (4) *confirmation* of the information revealed, (5) *localization* of suspected contacts, (6) *investigation* to determine whether the suspect is infected, and (7) *verification* of the infected contact as the source of infection.

Most published studies relating to contact investigation have dealt with the ultimate success of the procedure in terms of infected persons found per original case. Few attempts have been made to analyze the effectiveness of various types of efforts in achieving the desired end in investigations of this type. Packer, McGinnes and Puffer<sup>53</sup> have sought to determine the efficacy of the various technics applied to contact investigation. In their experience, a home visit in which the contact was interviewed was successful in 81.3 per cent of cases. When the contact was not seen but some one else in the household was interviewed, the percentage of success dropped to 56.0 per cent. Telephone calls to the contact's employer were quite successful (58.3 per cent), and telephone calls to the contact achieved 54.3 per cent success. Letters were less useful, being successful for 47.2 per cent of addresses. A study of the cumulative success of epidemiologic efforts on contacts shows that when success is achieved it usually

50 Burow, F. P. Fluctuation of Venereal Disease Incidence Among Alien Seamen, *Ven Dis Inform* 24:45 (Feb.) 1943.

51 McIlhany, L. W., and Smith, D. C. Epidemiologic Studies in Syphilis, *Virginia M Monthly* 70:130 (March) 1943.

52 Goodman, H. Essential Steps for Successful Epidemiology in Syphilis and Other Communicable Venereal Diseases, *Am J Syph, Gonorr & Ven Dis* 27:275 (May) 1943.

53 Packer, H., McGinnes, G. F., and Puffer, R. R. A Field Study of Contacts of Syphilis Cases, *Ven Dis Inform* 23:323 (Sept.) 1942.



results from the first two or three efforts, with 71.4 per cent of the ultimate successes following the first effort (table)

Development of the venereal disease control program in the city of New York has resulted in the evolution of certain practical procedures and technics, which are detailed by Rosenthal and Goodman<sup>54</sup> Effective case reporting with careful epidemiologic follow-up of infectious patients forms the cornerstone of the control program, although rehabilitation of infected selective service registrants and efforts to facilitate control of syphilis in industrial establishments have received considerable attention A central tabulating unit has been found valuable in case holding and in contact investigation

*Case Holding*—A problem of control of syphilis more or less peculiar to that disease is the difficulty of keeping patients under treatment until adequate treatment has been effected The reasons why patients become delinquent in their treatment and modalities of restoring them to treatment are exemplified by an analysis of 5,130 delinquencies<sup>55</sup>

The reasons for delinquency were most often leaving the country, illness other than that due to treatment, working at the time of clinic sessions and

*Successful Contact Investigations According to the Number of Epidemiologic Efforts Made (Packer, McGinnes and Puffer<sup>53</sup>)*

	Number of Contacts	Number of Successes	Cumulated Successes		
			Number	Per Cent of Total Contacts	Per Cent of Total Successes
Total	1,059	846	846		100.0
First effort	1,059	604	604	57.0	71.4
Second effort	306	157	761	71.9	90.0
Third effort	108	52	813	76.8	96.1
Fourth effort	45	23	836	78.9	98.8
Fifth effort	13	7	843	79.6	99.6
Sixth effort	5	3	846	79.9	100.0

reactions to treatment In all, 38.2 per cent of these delinquent patients ultimately were restored to treatment The type of follow-up effort that achieved the greatest success was a home visit in which the patient himself was interviewed Of the patients who were restored to treatment by follow-up effort, 89 per cent were restored after the first effort and 98 per cent after the second effort Additional efforts did not prove feasible

Since Jan. 1, 1936, the law for premarital serologic tests for syphilis has been in effect in Connecticut Talbot<sup>56</sup> has analyzed the results of the legal requirement for premarital blood tests over a seven year period In this period, 750 men and 690 women were found to have positive reactions—a prevalence rate for both sexes of 14.1 per thousand marriages About 50 per cent of the persons applying for marriage licenses who had positive serologic reactions and were given a diagnosis of syphilis were not aware of the infection Since the law has been in operation, the number of cases of congenital syphilis in the state has decreased progressively The marriage rate per thousand population decreased

54 Rosenthal, T., and Goodman, H. Epidemiologic Methods Used in the Control of Venereal Diseases in New York, New York State J. Med. **42**: 1346 (July 15) 1942

55 Packer, H., McGinnes, G. F., and Puffer, R. R. A Study of Delinquent Syphilis Patients in the Memphis-Shelby Venereal Disease Control Program, Ven. Dis. Inform. **23**: 289 (Aug.) 1942

56 Talbot, H. P. Blood Tests for Syphilis on Premarital Applicants for Seven Year Period, 1936-1942, Connecticut Health Bull. **57**: 70 (March) 1943



in 1936, the first year the law was in effect, but since then has increased steadily, to become more than twice as great in 1942 as in 1932

The author considers the law effective as a case-finding procedure, as setting a precedent for physicians and furnishing an incentive for making routine serologic tests, as a measure for reducing the incidence of congenital syphilis, and as a means of educating the general public about syphilis

Mahoney<sup>57</sup> outlines the approved manner of complying with the provisions and requirements of the statutes in force in various states in regard to premarital blood testing. Twenty-nine states require premarital blood tests. Those states which do not are Alabama, Arizona, Arkansas, Delaware, District of Columbia, Florida, Georgia, Idaho, Kansas, Maryland, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Mexico, Oklahoma, South Carolina and Washington. Of the states demanding a premarital blood test, all will accept a single standard or acceptable test with the exception of Pennsylvania, which requires that both a flocculation and a complement fixation test be employed.

The following states will accept reports of serologic tests performed in the laboratories of the armed services and of the United States Public Health Service and will permit the commissioned medical officers of the services to collect the specimens of blood and perform physical examinations. California, Colorado, Indiana, Iowa, Michigan, New Jersey, New York, Rhode Island, South Dakota, Utah, Vermont, and Virginia. Information regarding the requirements of the other states demanding premarital tests is variable. A brief digest of the requirements of each is given in the present article.

*Serologic Surveys*—In control of syphilis, methods of case finding which have a wide field of application and which bring under treatment a large number of infectious persons are those which should be stressed. As Packer<sup>58</sup> points out, the method or combination of methods which will achieve this end most effectively in any community can be determined best by actual application and subsequent analysis of the results. Each community has its own peculiar population characteristics and its own problems with regard to case finding. The author's experience in Memphis and Shelby County, Tenn., indicates that in areas of high prevalence of syphilis, particularly when a considerable proportion of the population is Negro, the group approach through routine examination of large sections of the population should be stressed.

Serologic surveys have been widely used as a means of discovering cases of syphilis. Such surveys provide a method for determining the prevalence of syphilis in selected population groups. They serve also as a valuable medium of education. Many different groups have been surveyed by routine blood tests. In surveys among labor groups the usual procedure is for the employer to act as the sponsoring agent. Koch and Merrill<sup>59</sup> report the results of a survey in which the approach was made through the labor organization without reference to employer groups. Serologic tests were entirely voluntary, and of the total union membership in the areas surveyed, only 4 per cent had tests made. Of 8,027 persons tested, 336 (4.1 per cent) were found to have positive serologic reactions. Of 133 of this number fully studied, 71.5 per cent were persons whose infections

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57 Mahoney, J. F. Requirements of Premarital Legislation as They Apply to the Laboratories and Commissioned Medical Officers of the Armed Services and of the United States Public Health Service, *Ven Dis Inform* **24** 105 (April) 1943.

58 Packer, H. A Comparison of Case-Finding Methods in a Syphilis Control Program, *Ven Dis Inform* **23** 440 (Dec) 1942.

59 Koch, R. A., and Merrill, M. H. Serologic Survey Among Labor Unions in Northern California, *Ven Dis Inform* **23** 317 (Sept) 1942.

were newly discovered. The costs of the survey were recorded. For each previously unknown case of syphilis discovered the cost was approximately \$42.

Because of wartime demands for blood plasma, more serologic tests for syphilis than ever before are being performed on prospective blood donors. Noting the case finding value of these tests, Frye, Keller, and Kampmeier<sup>60</sup> have sought to determine by the questionnaire method what is being done about the donors found to have positive or doubtful reactions. Of 603 hospitals from which replies to the questionnaire were received, 65 per cent did not test blood donors for syphilis before their blood was used. Of those hospitals testing donors, 12.5 per cent had no method for notification of the donors found to have positive or doubtful reactions. The person or agency responsible for notifying donors and the method of notification varied according to the size of the hospital and the type of administrative control. Most commonly, responsibility for notification of donors devolved on the private or attending physician.

The findings indicate the need in many hospitals for a more definite system whereby prospective blood donors found to have positive or doubtful serologic reactions for syphilis may be notified of the result of the test in order that they may receive prompt and adequate examination and treatment. The authors recommend that hospitals report such persons to the responsible health department as suspected of having syphilis. The health department then could arrange for proper disposition.

*State Consultation Service*—When organizations for control of syphilis depend to a great extent on the private practitioner to uncover most and treat about half of the existing persons with syphilis, any procedure that holds promise of improving their role must be seriously considered. The provision of consultation service along definitely formulated lines offers an opportunity in this regard. Because of the magnitude of the task, the health department is the proper agency to assume the responsibility of providing the service.

Within the past few years there has been a trend toward the creation or improvement of existing facilities for furnishing syphilis consultation services to private physicians. Four state health departments already have provided this service by incorporating full time consultants within their divisions of venereal disease control. Kroll<sup>61</sup> has analyzed the operation and results of this service in the state of New York. An intensive consultation service properly decentralized and actively promoted gave promising results. Of 826 physicians apprised of the availability of the service by letter, 105 responded by indicating their desire for consultation. Assistance was readily accepted by an additional 218 physicians of a total of 334 who were visited without invitation.

Questions most frequently asked of the consultants were those involving late latent syphilis, drugs and neurosyphilis. Questions on early syphilis, congenital syphilis, interpretation of serologic reports, infectiousness, pregnancy and cardiovascular syphilis were frequent in the order named.

*Role of the Pharmacist in Syphilis Control*—An editorial writer,<sup>62</sup> discussing the role of the pharmacist in control of venereal disease, states

The pharmacist himself is more aware than anyone else of his responsibility to the community in assisting the health authorities in the urgent task of bringing venereal disease

60 Frye, W. W., Keller, A. E., and Kampmeier, R. H. The Hospital and the Syphilis Problem in Prospective Blood Donors, *J. A. M. A.* **121**: 182 (Jan. 16) 1943.

61 Kroll, M. M. A State Syphilis Consultation Program for Private Practitioners, *Am. J. Syph., Gonorr. & Ven. Dis.* **27**: 63 (Jan.) 1943.

62 Venereal Disease Control and the Pharmacist, editorial, *New England J. Med.* **227**: 888 (Dec. 3) 1942.

patients under proper treatment

Through his professional organizations, notably the American Pharmaceutical Association, and with the cooperation of the American Social Hygiene Association, the pharmacist has demonstrated a willingness to take an active part in the national program for the control of syphilis and gonorrhea

By participating in the program for venereal-disease control, the pharmacists of this country will strengthen public confidence in their profession. At the same time they will know personally that their efforts are being given toward the elimination of the venereal-disease scourge, both for the best interests of the civilian population and for the greater fighting efficiency of the armed forces of the Nation

#### SYPHILIS AND THE WAR

*Wartime Venereal Disease Control—Civilian Aspects*—In the wartime program for control of venereal disease, Americans are, as Vonderlehr<sup>63</sup> indicates, well prepared, since the fundamental principles of control already have been established. It remains necessary, however, to apply these principles promptly and fully, that the campaign be aggressive and unified and that there be unanimous support of the public, of the medical profession and of the public health groups

As minimal services, the health department must supply collection and analysis of morbidity data, adequate laboratory services, an effective control program for industry, organization and supervision of clinic services and epidemiologic procedures, adequate follow-up services for men examined under the Selective Service System, utilization of routine serologic tests as a case finding procedure, development by means of an effective educational program of the support and understanding of the public and of all interested scientific groups, and encouragement and support for law enforcement agencies in the repression of prostitution

The physician who manages patients with venereal disease privately or in the clinic must provide for treatment to obviate infectiousness and for the examination of contacts. The weakest links in the venereal disease control program, according to the author, are case finding through routine epidemiologic procedures, and case holding until the treatment has been completed. A greater number of adequately trained follow-up workers clearly is needed

The role of the Army and the Navy in control of venereal disease includes provision for qualified professional personnel, abolition of punitive measures for the acquisition of venereal disease, modification of the policy of compulsory hospitalization for uncomplicated venereal disease, educational measures, supervision of prophylaxis, and cooperation with other interested groups within the post and in the civilian community. The public-spirited citizen interested in social hygiene also contributes to the success of the program, chiefly by fostering general understanding and support through educational methods

Vonderlehr<sup>64</sup> further describes some of the problems occasioned by the venereal diseases in time of war. Provisions for early diagnosis and facilities for the institution of prompt treatment exist in almost all areas with full time local health services, but a scarcity of trained personnel has handicapped the follow-up program. The routine serologic examination of selectees has placed an additional strain on epidemiologic facilities, for the pressing need for men necessitates prompt rehabilitation. It is the obligation of the health officer and the physician in private practice to bring the infected selectees under treatment. Vonderlehr says

In all history, war has opened the gates to pestilence. Venereal disease strikes first, and its wounds are often the last to heal. At the present time, the United States is better prepared

63 Vonderlehr, R. A. Individual Support in the Unified Wartime Venereal Disease Control Program, *Am J Syph, Gonorr & Ven Dis* **26** 661 (Nov) 1942

64 Vonderlehr, R. A. The Impact of the War on the Venereal Disease Problem, *New England J Med* **227** 203 (Aug 6) 1942

than ever before to wage an effective campaign against gonorrhea and syphilis. Tolerated prostitution and failure to apply promptly modern medical knowledge are the most vulnerable points in this field of medicine.

Stressing the relationship between the practicing physician and the health department in control of venereal disease in wartime, Vonderlehr<sup>65</sup> indicates that the emergency problem is to get infected selectees and their contacts in condition for military service and essential war work in the shortest time possible. The health department should teach the public the causes, the prevention and the treatment of venereal diseases, provide laboratory services and drugs, keep persons known to be infected under treatment by private physicians or at clinics, seek out persons who are sources of infection and bring them under treatment, treat those who cannot afford to pay and refer to practicing physicians all who can. The physicians, for their part, are asked to educate and treat their patients, to be ever on the alert for contacts and to report lapses from treatment as quickly as they occur.

Emerson<sup>66</sup> pessimistically writes

We may expect in the civilian as in the military population an increase in the direct and indirect effects of syphilis in this wartime unless there is something like a revolution in the social attitudes toward venery. Every syphilitic person is an obstruction to military and civil preparedness for national defense.

The author notes that the specific death rate among "our industrial and wage earning men and women and their families," the death rate per hundred thousand from syphilis, has decreased from 19 to 9.0 in the past twenty-five years. The material from which these statistical data were derived are not apparent from the article, but to the reviewers it seems unlikely that such precise figures can be delineated.

According to Aselmeyer,<sup>67</sup> the two conditions resulting from the war which overshadow other considerations in the venereal disease control program are (1) the extraordinary mobility of both military and civilian populations and (2) the acute shortage of professional personnel in civilian areas. Outlining the venereal disease control measures at present available, the author stresses the role of the civilian physician, stating

The war will bring to the physicians who remain in their communities overwhelming tasks comparable with the experiences of our colleagues in the Army and Navy. One of the first tasks commanding the doctor's attention is the control of venereal diseases in his community. No matter how well we plan and execute a national attack, no matter how far we stretch the available funds, the control of these diseases is in the hands of the local physicians of the United States. Neither the federal government nor the local health department nor the private physician, however, can accomplish this great task alone. Together, we can bring venereal diseases under control and keep them under control.

Certain problems concerned with the control of venereal disease in wartime have been discussed by Stokes,<sup>68</sup> to whom the application of recent scientific discoveries to the control program seems paramount. The fallibilities of serodiagnostic tests and of dark field examination, intensive arsenotherapy, rapid cure of gonorrhea with sulfonamide compounds and mechanical and chemical prophylaxis are all discussed, together with the problem of morale as it relates to venereal disease.

65 Vonderlehr, R. A. Public Health Control of Venereal Diseases in the District of Columbia, *M. Ann. District of Columbia* **11** 471 (Dec.) 1942.

66 Emerson, H. Civilian Health in War Time, *J. A. M. A.* **119** 1389 (Aug. 22) 1942.

67 Aselmeyer, A. J. Civilian Measures for the Control of Venereal Diseases in World War II, *J. A. M. A.* **120** 880 (Nov. 21) 1942.

68 Stokes, J. H. The Wartime Control of Venereal Disease. Problems in the Application of Recent Scientific Discoveries, *J. A. M. A.* **120** 1093 (Dec. 5) 1942.

*Rehabilitation of Selectees*—An inquiry<sup>69</sup> to determine how many selectees rejected because of venereal disease have been put under treatment and after treatment have been inducted into military service has been made by the United States Public Health Service. Thirty-three states report that of the 178,884 syphilitic selectees who were rejected, 114,337 (64 per cent) were under treatment on Dec 31, 1942. Of these, 81,632 had been placed under treatment as a result of the selectee examination, and the remaining 32,705 had already been receiving therapy. The states report that 5,777, or 5 per cent of the total number under treatment, have been inducted.

*Role of the Public Health Nurse*—The role to be played by the public health nurse in wartime control of venereal disease has been described by Pearce.<sup>70</sup> As increasing numbers of physicians are drawn into the armed forces, nurses will be called on to perform under medical supervision more of the duties and functions normally carried out by doctors. The demand for nurses will be augmented with the development of artificial fever therapy and of rapid treatment schedules for antisyphilitic therapy.

To insure economical use of nursing personnel, Miss Pearce recommends (1) the release of the public health nurse from many clerical and housekeeping duties through the use of volunteer or paid clinic assistants, (2) the employment of inactive nurses to assist with treatment, (3) the assignment of a minimum number of public health nurses or medical social workers, (4) increased emphasis on special consultative and educational services.

Because of the increased importance of venereal diseases in time of war, Burke<sup>71</sup> believes that all public health nurses should spend at least part of their time in tracing contacts. Discussing the objections which have been raised to the use of general public health nurses in venereal disease control, she concludes that it is highly desirable for the general nurse to supplement the work of the specialized nurses already in the field.

Of paramount importance in wartime venereal disease control are follow-up and rehabilitation of selectees rejected for armed service because of syphilis. The ways in which the nursing profession can assist in this work are discussed by Burns.<sup>72</sup>

In interviewing the patient with syphilis, it is important, according to Bailey,<sup>73</sup> to establish between the patient and the clinic a rapport on which lasting confidence may be developed. The patient must sense a regard for his own welfare as well as for the welfare of others. When the persuasive approach has won the patient's confidence, he will cooperate in getting his contacts examined.

*Wartime Venereal Disease Control: Military Aspects*—An extensive and important review concerned with the prevention of venereal diseases in the Army of the United States has been made by Siler.<sup>74</sup> The first section of this monograph is a statistical review of the incidence rates and prevalence of the venereal infections in the Army. The second section concerns the preventive measures initiated within the Army in years past for the control of these diseases. Of greatest interest

69 U S Public Health Service, Association Notes, Mil Surgeon **92** 675 (June) 1943

70 Pearce, D. Major Public Health Battlefront, Pub Health Nursing **35** 8 (Jan) 1943

71 Burke, M. A. Extra-Familial Contact Tracing, Pub Health Nursing **35** 15 (Jan) 1943

72 Burns, A. Syphilis Follow-Up Among Selectees, Pub Health Nursing **35** 28 (Jan) 1943

73 Bailey, F. G. Interviewing the Syphilis Patient, Pub Health Nursing **35** 47 (Jan) 1943

74 Siler, J. F. The Prevention and Control of Venereal Diseases in the Army of the United States of America, Army M. Bull., May 1943, no 67

are Siler's comments on the practical value of the various control measures which have been tried during the past thirty years

According to Turner,<sup>75</sup> the present venereal disease rates in the Army are substantially below those of World War I and only slightly higher than the rates for the preceding ten years of peace, but the rate of 40 per thousand for 1941 and the somewhat lower rate for 1942 are still excessive. There are still too many soldiers being infected and too many selectees reporting for duty with venereal disease. During the past two and a half years many important steps have been taken to mobilize the health forces of the country, both military and civilian, to meet this problem. In 1940, the so-called eight point agreement was signed. In the same year, the United States Public Health Service assigned a liaison officer to the headquarters of each service command to aid in the control of venereal diseases. In April 1941, the Social Protection Section, Defense Health and Welfare Services, was organized, and later the Interdepartmental Liaison Committee on Venereal Diseases was created. This committee comprises representatives of the Army, the Navy and the Public Health Service, the Social Protection Section and the American Social Hygiene Association. Early in 1942 authorization was given for the assignment of specially trained venereal disease control officers to major headquarters of the Army. Never before in the history of this country has the stage been so well set for a concerted attack on these diseases.

It has been learned that the control of venereal disease among troops must be a collaborative effect between military and civilian authorities. The problem is primarily one of preventive medicine, the immediate task being to keep soldiers and workers well and effective. It is agreed that commercialized prostitution is a breeder of venereal disease and should go. Remarkable progress has already been made during the past two years in suppressing the most obvious and perhaps the most dangerous type of prostitution, that centered in the redlight district and the brothel.

It is becoming increasingly evident that other forms of social misbehavior are beginning to play a prominent role in the spread of venereal disease. An ever increasing proportion of soldiers are being infected by pick-ups, tavern and dance hall girls and the like. It is difficult to know just who is and who is not a prostitute. The important element in the picture is not the individual woman but the business structure which makes it possible for a girl to expose numerous contacts. Turner says

To express this idea, Dr. Donald Williams, of British Columbia, has coined a new phrase, "the facilitation process." He maintains, and rightly, I believe, that we should cease speaking of prostitution in this connection, and concentrate our social and legal efforts on finding and suppressing the "facilitators"—the tavern keepers, the bell boys, the taxi drivers, and the owners of these businesses who facilitate the spread of venereal disease.

This approach appeals to Turner, who has been disturbed by the tendency in some places for law enforcement officials, often at the instigation of those concerned in control of venereal disease, to engage in a determined hunt for young girls to the exclusion of the more important job of getting at the facilitators.

A program for venereal disease control in a military camp is outlined by Lieberman,<sup>76</sup> who discusses education, prophylaxis, case finding, treatment, cultivation of cooperation with civilian agencies and establishment of cooperative relations with the military police and recommends certain desirable administrative measures

75 Turner, T. B. Some Aspects of Venereal Disease Prevention in Wartime, *J. Social Hyg.* 28:518 (Dec.) 1942.

76 Lieberman, B. A. An Effective Military Venereal Disease Control Program, *War Med.* 3:174 (Feb.) 1943.

Worthy of special comment are the data presented on the efficiency of station prophylaxis. The author states

Statistics available to me covering approximately 500,000 troops for the first half of 1942 indicate that only 0.69 per cent of prophylactic treatments were ineffective in preventing the development of venereal disease in exposed soldiers

It is perhaps pertinent to object to the inclusion of the infected soldier's name on the contact report forwarded to the civilian health department. Moreover, the practice of collecting information on contacts at prophylactic stations should be condemned, since it tends to dissuade men from taking prophylaxis. The program outlined, however, is one which should effectively lower the incidence of venereal infections in military establishments.

*Educational Talks to Service Personnel*—All medical officers are charged with instructing the entire personnel regarding the nature of venereal disease and warning them of the dangers therefrom. One of the most effective measures for education on venereal disease is a well planned and well delivered man-to-man discussion by the medical officer himself.

Reynolds<sup>77</sup> discusses the salient features of educational talks to service personnel on venereal disease. The most effective appeals are to the men's sense of reasonableness and to their fear of the consequences of venereal infection. In outline, the talk should include an appropriate introduction, a brief description of the genitoinfectious diseases, discussion of the common misconceptions about these diseases, explanation of how and from whom venereal infections are acquired and spread, complete details of how they may be prevented and instruction on what to do if infection is suspected. A catalog of venereal disease educational materials available to medical officers is appended.

*Chemical Prophylaxis*—It is well established that venereal infections can be prevented in most instances by proper chemical prophylaxis. This fact is amply attested by the experiences of the Army and Navy. On the other hand, the failure of chemical prophylaxis in American civilian groups apparently is taken for granted. Civilians fail to avail themselves of prophylaxis because of inconvenience, fear of publicity or embarrassment, and lack of compulsion.

Frantz<sup>78</sup> believes successful chemical prophylaxis of the venereal diseases in the American civilians to be highly desirable. In August 1941, the Sacramento (Calif.) City Health Department opened an experimental prophylaxis station for civilians and military use. Between Aug. 14 and Dec. 14, 1941, 4,163 standard chemical prophylactic treatments were administered. Male civilians received 2,062 (49.5 per cent) and members of the armed forces 2,101 (50.5 per cent) of these treatments. No coercive measures were used. Both the civilian and the soldier attended the same station concurrently and were served by the same attendant. Certain minimal data were secured from each person receiving prophylaxis: initials, time of exposure, time of prophylaxis, name of the consort and place of exposure. Ninety-six per cent of the group named a prostitute as the consort. The community reaction to the establishment of the station was favorable. Hotels, theaters, gasoline stations and civic institutions have permitted the posting of advertising material in their rest rooms.

Control of venereal disease in the armed forces depends to a high degree on effective chemical prophylactic treatment that may be used after sexual inter-

77 Reynolds, F. W. Suggestions to the Naval Medical Officer for Talks on Venereal Disease, U. S. Nav. M. Bull. **41** 889 (May) 1943.

78 Frantz, R. Civilians, Soldiers and the Chemical Prophylaxis of Venereal Diseases, Ven. Dis. Inform. **23** 286 (Aug.) 1942.



course One of the difficulties with this treatment is that it may not be available near the place where the exposure occurs This fact, together with certain other objectionable features of "station" prophylaxis, has led medical officers to study the use of prophylactic kits

Pelzman and Still<sup>79</sup> report that the prophylactic packet used at Fort Belvoir, Va., contains a soap-impregnated wash cloth, a tube containing silver picrate jelly (0.25 per cent), a tube with a mild mercurous chloride ointment and a cloth bag to protect the clothing In their small series of 374 soldiers who were given prophylactic treatment with these packets, no infections with syphilis developed within eight weeks The authors believe that packet prophylaxis of venereal infection compares favorably with prophylactic treatment administered at prophylactic stations

*Contact Reporting and Examination*—An important phase of control of venereal disease is the discovery of unrecognized infections, especially those in the early and communicable stage Experience has shown that the search for unrecognized infections is especially productive among persons who have had intimate contact with infected persons

A summary of contact reporting from the point of view of the medical officer is made by Reynolds<sup>80</sup> The proper reporting of the sexual contacts of service personnel infected with venereal disease presupposes a knowledge of the reasons why the names of contacts are withheld and requires a tactful sympathetic approach to the patient Care must be taken to differentiate "source of infection" from "sexual contacts" A contact is defined as a person whose exposure to a patient during the period of possible infectiousness has been sufficiently intimate as to subject either to risk of acquiring the disease Reports should contain as much information as possible about each contact and should be forwarded to the responsible civilian authorities as soon as practicable

An analysis of the data obtained by questioning infected service personnel at a large Army post is summarized by Barnes<sup>81</sup> Of 1,032 patients with venereal disease, 26 per cent divulged the full name of the sexual partner, and an additional 15 per cent gave the first name only The majority (50 per cent) of contacts named were "pick-ups" or free-lance prostitutes, and only 26 per cent were girls in organized houses of prostitution Hotels most often were the places where exposure occurred, with automobiles and private homes next in order of frequency Gonorrhea occurred five times as often as syphilis, and 9 of each 10 men acquiring one or the other infection had neglected to take prophylactic treatment Over half of the men said they had had a prior infection in civil life

The information obtained was used to determine where most of the infections were originating It served as a guide to the need for additional prophylactic stations and made it possible to call to the attention of the civil police authorities the need for enforcement of local laws against commercialized and clandestine prostitution

Effective control of venereal diseases in the armed forces requires close cooperation between the service organizations and civilian health agencies In no way is this mutual assistance better exemplified than in the epidemiologic investigation of the sexual contacts reported by infected service personnel

79 Pelzman, I. A., and Still, J. W. Packet Type of Kit for Venereal Disease Prophylaxis Preliminary Report Concerning Its Use, *War Med* 3:474 (May) 1943

80 Reynolds, F. W. Contact-Reporting in Venereal Disease Control A Function of the Medical Officer, *Mil Surgeon* 91:432 (Oct) 1942

81 Barnes, A. Sources of Venereal Infections at an Army Post Study of 1,032 Cases at Fort Leonard Wood, *Mil Surgeon* 92:257 (March) 1943



A novel experience in contact questioning is reported by Howard, Vahey and Wetherby<sup>82</sup> In Massachusetts, health department nurses trained in epidemiologic methods were allowed to enter Army camps and Navy stations to question infected personnel as to their sexual contacts This expedient proved effectual, for whereas previously medical officers had obtained adequate information in only 13 per cent of the cases, the public health nurses were successful 60 to 83 per cent of the time

The data so gathered were analyzed and utilized by the health department for further study When the information implicated prostitution or an allied activity requiring police control, it was forwarded to the responsible police agency Of 193 contacts followed by the nurses, 89.6 per cent were found and placed under medical observation, 36.3 per cent of the 157 referred to the police were apprehended Two hundred and seventy-three contacts were referred to other state health departments, and 27.5 per cent were found successfully (evidence of reasonably good cooperation among the state health departments)

An analysis<sup>83</sup> of venereal disease contacts reported from four states in the Ohio River Valley for the period ending July 31, 1942 suggests that the size of a city contributes more to the frequency of infection among military personnel than does its proximity to an Army camp The data indicate that the highest rate is among cities of 100,000 population and over, and that rates in smaller cities decrease with the size of the city Some of the largest cities were as much as 150 miles (240 kilometers) from a military establishment but were reported, nevertheless, as localities where many infections were contracted Thus the role of modern transportation facilities is indicated and the necessity for a nation-wide control program emphasized

#### SYPHILIS IN FOREIGN COUNTRIES

*England*—In England,<sup>84</sup> a new defense regulation (33B) extends the powers available under the present law for the treatment of venereal diseases and enables compulsion to be applied in carefully defined circumstances

Hitherto the arrangements for the treatment of these diseases have been based on voluntary attendance for treatment The new regulation leaves the voluntary basis unchanged, but provides for compulsion, where necessary, to bring under treatment those persons who are impervious to methods of education and persuasion and who refuse to attend voluntarily for treatment although known to be infected and to be spreading infection

Commenting on England's new Defense Regulation 33B, whereby persons suspected of spreading venereal disease are compelled to undergo examination and treatment, the London correspondent of *The Journal of the American Medical Association*<sup>85</sup> writes

In contrast with the compulsory treatment of venereal disease in other countries, the arrangement in this country has been based exclusively on voluntary attendance This is in accordance with that respect for the freedom of the individual which is characteristically British But here the obvious criticism is that what is granted is freedom to spread disease The voluntary system has had a large measure of success, and before the war the incidence

82 Howard, E. B., Vahey, V. V., and Wetherby, U. V. Epidemiologic Investigation of Syphilis and Gonorrhea in the Army and Navy in Massachusetts, *Ven. Dis. Inform.* **24**: 1 (Jan.) 1943

83 Venereal Disease Contacts, Association Notes, *Mil. Surgeon* **91**: 712 (Dec.) 1942

84 Chronic Sources of Venereal Infection: Power to Enforce Treatment, *War Medicine Series, Brit. M. J.* **2**: 616 (Nov. 21) 1942

85 Compulsory Treatment for Venereal Disease, *Foreign Letters (London)*, *J. A. M. A.* **121**: 142 (Jan.) 1943

of venereal disease was low and compared favorably with that of other countries. The war has now accustomed us to limitation of our freedom in many directions, and for good reason a new defense regulation introduces compulsion for the treatment of venereal disease in certain carefully defined circumstances.

The regulation provides that persons named by two separate patients under treatment as the suspected source of their infection can be required, by notice served on them by the health officer of the district in which they live, to attend for examination, and if necessary, for treatment by a "special practitioner," and to continue treatment in accordance with his directions until they are certified as free from venereal disease in a communicable form.

Those interested in details of Regulation 33B are referred to a comprehensive discussion of the legal aspects of the act by Shannon<sup>86</sup>.

*Puerto Rico*—According to Quintero,<sup>87</sup> syphilis is about two and a half times as prevalent in Puerto Rico as in the continental United States. The socioeconomic structure of the island is considered important in this high rate of prevalence. Overcrowding, poverty and illiteracy all are factors. Under the existing circumstances, a high incidence rate of syphilis among service personnel stationed in Puerto Rico is to be expected. To meet the situation, the author recommends expansion of the control program in its medical, educational and legal aspects. Intensification of the program for follow-up of reported contacts, isolation of patients for intensified treatment and repressive measures against prostitution are advocated.

*Soviet Russia*—A report of the Anglo-Soviet Medical Council<sup>88</sup> says that venereal diseases were widespread in tsarist Russia, especially among the population of the national minorities. In Moscow in 1914 there were for every 10,000 people approximately 388 patients with venereal disease, of whom 56.9 per cent had been infected by prostitutes. Incomplete data indicate that in the country as a whole there were 76.8 persons with syphilis per 10,000 people.

With the advent of Soviet power, one of the earliest public health measures was to institute a campaign against venereal diseases. There were two main directions of attack, against venereal diseases as such and against prostitution as an institution. From the Soviet point of view, prostitution is regarded as being primarily due to economic causes, and the campaign to abolish it was directed against the institution, not the individual. Two new laws were passed, one making the infecting of a sexual partner punishable by up to three years' imprisonment and the other making treatment compulsory. Treatment centers were established, graduate courses of instruction for physicians were organized, and serologic tests were used widely. As a result of these measures, there has been a considerable decrease in the incidence of infection throughout the country.

*Australia*—Statistics prepared at the 120th Australian Special Hospital over a period of eighteen months show that 85 per cent of the patients infected with venereal disease contracted their infection from amateur sources and 15 per cent from professional prostitutes. The great majority of patients contracted the disease while on leave in one of the larger cities.

As to the prevention of venereal disease among the Australian armed forces, Gibson<sup>89</sup> says that Army medical officers are being given lectures by specialists at the Army School of Hygiene and the School of Public Health and Tropical Medicine. Lectures are also given to combatant officers and noncommissioned

86 Shannon, N. P. The Compulsory Treatment of Venereal Diseases Under Regulation 33B, *Brit J Ven Dis* **19** 22 (March) 1943.

87 Quintero, E. Preliminary Report on Local Venereal Diseases Relative to the Puerto Rico Encamped Military Forces, *Bol Asoc méd de Puerto Rico* **35** 180 (May) 1943.

88 Anti-Venereal Measures in the Soviet Union. Report from the Anglo-Soviet Medical Council, *Brit J Ven Dis* **19** 39 (March) 1943.

89 Gibson, N. M. Control of Venereal Disease in the Army, *M J Australia* **2** 290 (Sept 26) 1942.

officers, who in turn are expected to impart this knowledge to the troops of their units. A meeting attended by the commonwealth and state authorities, together with the representatives of all services, including the United States Army, is held once a month to discuss prophylaxis and treatment as well as coordination between the services.

Condoms and chemical prophylactic kits are issued free to all troops going on leave. The prophylactic packet contains two tubes, one containing 3 per cent mild protein silver jelly, and the other 33 per cent mild mercurous chloride ointment. Prophylactic stations have been established in all camps and nearby towns and cities. Special medical inspection is made of all troops entering the camp and before they go on draft, as well as at various times during their training. Soldiers found to be infected are evacuated to the 120th Australian Special Hospital. All soldiers in the Home Forces suffering from syphilis are discharged as medically unfit, since it is considered necessary to treat them for eighteen to twenty-four months.

*France*—According to *Transocean France* of March 16, 1943,<sup>90</sup> 2 000,000 Frenchmen have died from venereal disease during the past ten years, and some 5,000,000 Frenchmen are infected with syphilis today. Dr. Arthur Veines has declared that during the last three years alone infections have trebled.

Infant mortality in France during 1940<sup>91</sup> was 9.1 per cent. In the same year 25,000 stillborn children were delivered, a large percentage of these stillbirth cases being due to syphilis.

#### SYPHILIS AND INDUSTRY

*Control of Venereal Disease in Industry*—A venereal disease control program in industry involves cooperation among four groups: the employers, the employees, the physicians and the public health department.

The objectives of a venereal disease control program in industry, as outlined by an advisory committee to the United States Public Health Service, are reported by Anderson and his co-workers.<sup>92</sup> Responsibilities of the medical and public health professions include: case finding and disposition of all cases of venereal disease among workers in industry; the establishment of equitable policies for the employment of applicants and continuation of services of infected employees; and coordination of the community and industrial programs for venereal disease control. The objectives for the employees are to improve the physical condition of employees, to reduce the number of work days lost through illness or injury, to provide proper job placement for infected men, and to prolong and increase the earning power of employees by increasing life expectancy. For the employers, the program should reduce compensation costs, lessen work interruptions and labor turnover, enhance production by increasing the efficiency of workers and minimize those personnel problems which arise from syphilis and gonorrhea as causes of ill health and nervous instability.

Responsibility for the administration of the program should be shared by the industrial hygiene and venereal disease divisions of the state health department. The educational program should be integrated and correlated with the general program of health instruction. Examinations for venereal infections should be part of the general physical examination, and the results of the examination should be confidential.

<sup>90</sup> Public Health Under Hitler, J. A. M. A. **122** 451 (June 12) 1943.

<sup>91</sup> Public Health Under Hitler, J. A. M. A. **122** 516 (June 19) 1943.

<sup>92</sup> Anderson, O. L., Clarke, W., Dreesen, W. C., Hayhurst, E. R., Holmblad, E. C., and Peterson, C. M. Venereal Disease Control Program in Industry, J. A. M. A. **120** 828 (Nov. 14) 1942.

### In the opinion of the advisory committee

There is no reason for denying employment to an applicant or for discharging an employee because an examination has revealed evidence of syphilis or gonorrhea, provided

- 1 That the employee agrees to place himself under competent medical management
- 2 That, if the stage of the disease is infectious, employment should be delayed or interrupted until such time as a noninfectious state is established through treatment and open lesions are healed
- 3 That syphilis exists in a latent stage
- 4 That, when disabling manifestations exist which would render such individuals industrial hazards to themselves, other employees or the public, employment may be deferred or denied
- 5 That provision be made, whenever possible, for occupational readjustments of employees who develop disabling manifestations that do not incapacitate them from performing some type of useful work
- 6 That workers with syphilis in any of its stages, and regardless of past or present treatment status, should be excluded from areas of toxic exposure, and that those having cardiovascular syphilis or neurosyphilis should not be exposed to such physiologic stresses as extremes of temperature, strenuous physical exertion or abnormal atmospheric pressure
- 7 That workers with gonorrhea should be allowed to work only under special medical observation during the administration of sulfonamide drugs

In making educational material on venereal diseases available to industrial employees, Storey<sup>93</sup> believes the approach should be made through (1) plant facilities, (2) community facilities, (3) labor organizations, (4) courses or classes or schools that prepare prospective employees for skilled service in factories, and (5) public school and college student health programs

Stressing the dangers of ill advised and improperly directed attempts to extend control of syphilis to industry, Nelson<sup>94</sup> says

Any physician who has under his care an employable syphilitic, and the industrial physician in particular, holds in his hand the future of the infected with syphilis. In those industries in which the problem is handled intelligently (and it is comforting to know that the number is constantly increasing) sound medical advice deserves much of the credit. How soon the problem is to be solved in the others will depend upon whether the well-informed physician or the uninformed layman is to determine the medical policy. It is becoming nauseatingly tiresome to note the frequency with which lay officials and directors, not only of industry but of hospitals and institutions and public agencies, lay down the rules as to who shall be admitted to employment, and even as to who shall be admitted as patients, not on the basis of well-known medical fact, but on the basis of prejudice, taboo and popular misconceptions. If we cannot look to the medical profession for the correction of this intolerable situation, to whom, then, may we look?

### DRUGS

*Dichlorophenarsine Hydrochloride* — Dichlorophenarsine hydrochloride (3-amino-4-hydroxyphenyldichloroarsine hydrochloride) has been used experimentally in the treatment of syphilis at Vanderbilt University Hospital, and the results of the study are reported by Kampmeier and Henning<sup>95</sup>. Over four thousand injections were given to 251 syphilitic patients. After a single therapeutic dose 42 of 45 patients with infectious lesions had negative results of dark field examination within twenty-four hours. Healing of acute lesions was prompt, chancres healing within four weeks and secondary lesions within five weeks. Serologic reactions became negative at a time comparable to that with use of other arsenical preparations.

93 Storey, T. A. Educational Hygiene—Extension to Industrial Employees for the Control of Gonorrhea and Syphilis, *Indust Med* **11** 411 (Sept.) 1942

94 Nelson, N. A. Syphilis in Industry, *Am J Syph, Gonor & Ven Dis* **27** 73 (Jan.) 1943

95 Kampmeier, R. H., and Henning, H. B. Treatment of Syphilis with Chlorarsen, *Am J Syph, Gonor & Ven Dis* **27** 208 (March) 1943

No serious untoward reactions were encountered. Nausea, vomiting and diarrhea were the most common reactions. The study indicates that phenarsine hydrochloride is effective in acute syphilis, is attended by few reactions and may be used as an alternate drug for patients having reactions to other arsenical drugs.

Ninety-six patients with syphilis, 20 of whom had either primary or secondary syphilis, were given by Long<sup>96</sup> a total of 2,033 injections of dichlorophenarsine hydrochloride. The compound was used as a mechanical mixture of 1 part by weight of 3-amino-4-hydroxyphenyldichloroarsine hydrochloride and  $3\frac{1}{3}$  and  $\frac{1}{3}$  parts of sodium citrate added as a buffer. It is readily soluble in water, salt solutions and dextrose solutions. The arsenical portion of this mixture contains 25.8 per cent of arsenic, while the final mixture contains 5.96 per cent. When dichlorophenarsine hydrochloride is dissolved in water the  $p_H$  of the solution is approximately 5.2, and the chlorine atoms are hydrolyzed so that when the drug is injected it is essentially arsenoxide. The drug was found to be effective in the treatment of early syphilis. Spirochetes could not be found in primary lesions twelve hours after the first dose. Serologic tests of the blood for syphilis responded satisfactorily, there was a low incidence of abnormal spinal fluids among the patients with early syphilis. Toxic reactions were limited to mild gastrointestinal disturbances. None of the severe forms of toxic reactions were noted.

For a period of eighteen months dichlorophenarsine hydrochloride has been studied at the University of Pittsburgh. As to the chemistry and pharmacology of the drug, Guy, Goldmann and Gannon<sup>97</sup> say

Two single dosage forms of phenarsine [dichlorophenarsine] hydrochloride are available. The smaller dose contains 0.045 Gm. of 3-amino-4-hydroxyphenyldichloroarsine hydrochloride, which yields 0.0308 Gm. of the active principle, 3-amino-4-hydroxyphenylarsenoxide (arsenoxide). A dose of 0.04 Gm. of mapharsen yields exactly the same amount of active principle. The larger dose of phenarsine hydrochloride (0.068 Gm.) yields 0.047 Gm. of 3-amino-4-hydroxyphenylarsenoxide. This corresponds to 0.06 Gm. of mapharsen content of the active principle. Both phenarsine hydrochloride and mapharsen contain about 25 per cent trivalent arsenic.

Dichlorophenarsine hydrochloride in the dry form does not contain arsenoxide. This is of importance because this drug is more stable. Arsenoxide is formed by the chemical reaction which takes place in the ampule when distilled water is added to the drug. Mapharsen, which is arsenoxide hydrochloride hemialcoholate, becomes arsenoxide on the addition of water. The structural formulas are given for both reactions.

Toxicity tests were carried out according to the standard National Institute of Health procedures, with the following results:

Of 77 rats receiving 15 mg. per kilogram intravenously the percentage of survivals was 96, of 62 rats receiving 16 mg. per kilogram the percentage surviving was 85.5, of 74 rats receiving 18 mg. per kilogram the percentage was 71, of 18 rats receiving 22 mg. per kilogram the percentage was 61. The toxicity of phenarsine hydrochloride does not differ materially from that of the mapharsen.

Therapeutic activity was determined by curative tests on rats infected with *Trypanosoma equiperdum*.

Of infected animals treated with 0.375 mg. per kilogram of phenarsine hydrochloride, 30 per cent survived the 28 day observation period, of those receiving 0.4375 mg. per kilogram, 24 per cent, of those receiving 0.500 mg. per kilogram, 41 per cent, and of those receiving 0.625 mg. per kilogram, 61 per cent.

These results do not differ materially from those obtained with mapharsen.

96 Long, W. E. Treatment of Syphilis with Phenarsine Hydrochloride. Preliminary Report, Arch. Dermat. & Syph. **47** 226 (Feb.) 1943.

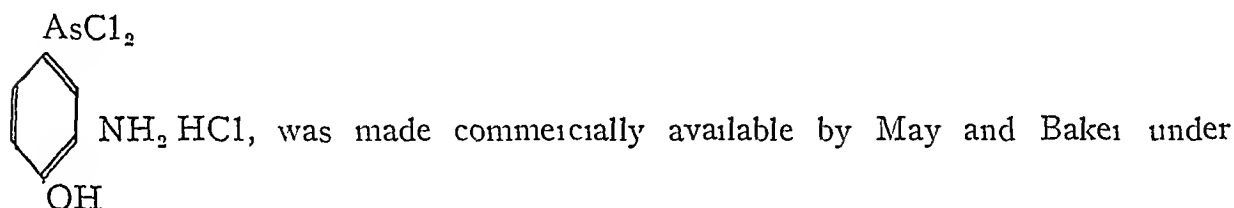
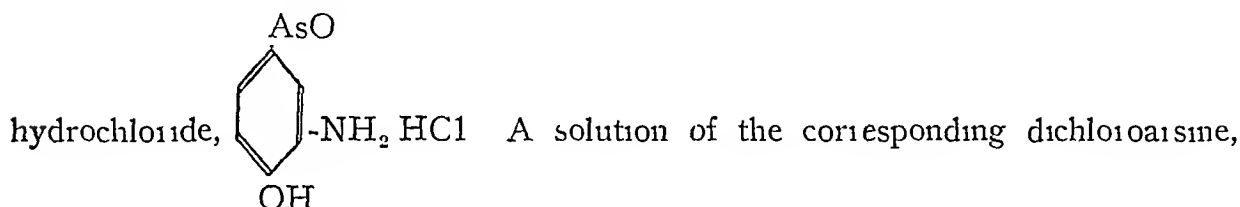
97 Guy, W. H., Goldmann, B. A., and Gannon, G. P. Phenarsine Hydrochloride in the Treatment of Syphilis. Preliminary Report, Arch. Dermat. & Syph. **47** 235 (Feb.) 1943.

The therapeutic index of both dichlorophenarsine hydrochloride and mapharsen is essentially the same, about 28

From January 1941 to July 1942, 233 patients were given 2,581 intravenous injections of dichlorophenarsine hydrochloride. In 4 patients with primary syphilis who were hospitalized for dark field studies, spirochetes disappeared from the lesions within twenty-four hours. Cutaneous lesions cleared rapidly, and in the majority of cases they had disappeared entirely in an average of fourteen days. No serious late reactions were encountered. A small percentage of the patients had mild symptoms, of nausea, vomiting, slight headache or pain in the arm, when the drug was administered slowly.

Clarification is desirable as to the confusion between mapharsen and dichlorophenarsine hydrochloride.

Mapharsen is the hemialcoholate of 3-amino-4-hydroxyphenylarsine oxide



the trade name halarsol some twelve years ago, before the development of mapharsen. The nonproprietary name dichlorophenarsine hydrochloride has been proposed for this compound for inclusion in the first supplement to the United States Pharmacopeia XII. The Squibb preparation clorsen and the Winthrop preparation phenarsine-Winthrop consist of this dichloroarsine packaged as dry powder with enough alkali to make a neutral solution.

Electrometric titrations on several dichloroarsines, including the Squibb product, show that when a solution of the dichloroarsine is brought up to *p*<sub>H</sub> 5 it is converted quantitatively to the arsine oxide. In other words, a solution of the dichloroarsine at *p*<sub>H</sub> 5 to 7, such as would be used therapeutically, is chemically identical with a solution of mapharsen. Provided only that the drugs are used in equimolar amounts, they must give therapeutically the same result. Data on toxicity in vivo and on spirocheticidal activity in vitro have proved this to be the case. Moreover, since the dichloroarsine has the same toxicity and treponemicidal activity, whether neutralized with sodium hydroxide, sodium carbonate or sodium citrate it seems clear that the nature of the base used has no demonstrable effect on the biologic activity of the resultant arsine oxide.

From the point of view of therapeutic activity, the several preparations are therefore identical. Dichloroarsines in general are more stable than the corresponding arsine oxides. To that extent an ampule containing the dry dichloroarsine, with enough dry alkali to make a neutral solution on the addition of water, might be more stable than an ampule of mapharsen, and the undesirable chemical changes sometimes noted in mapharsen ampules, evidenced by the discoloration of the powder, and believed to be due to oxidation of the aminophenol grouping, might thus be avoided or minimized.

*Trisodarsen*—Trisodarsen (trisodium arsphenamine sulfate) is the trisodium salt of 3,3' diamino 4,4' dihydroxyarsenobenzene N,N' di-methylene sulfonic acid. Over a period of eight years, a total of 6,852 injections of this drug has been given at the University of Pennsylvania Hospital. A resume of this experience is reported by Beerman, Pariser, and Gordon<sup>98</sup>. This study covers a total of 550 patients with syphilis. Of these, 234 had latent syphilis, 15 had late syphilis, 7 had congenital infections and 291 were in the early stages of the disease.

Under treatment with trisodarsen, lesions of early syphilis were found to heal rapidly, *S. pallida* disappearing in less than ninety-six hours. Forty-four per cent of the patients had untoward reactions to the drug. Of the severe reactions, there were 7 cases of exfoliative dermatitis, 4 cases of purpura, 5 of bleeding from the nose or mouth and 2 instances of aplastic anemia. The serologic response to treatment compared favorably with other trivalent arsenicals, and the number of clinical or serologic relapses was not unduly large. In spite of the high incidence of serious reactions, the drug is considered "promising" by the authors.

*Bismarsen*—A review of fourteen years' experience with the use of bismarsen (bismuth arsphenamine sulfanate) at the University of Pennsylvania is presented by Beerman, Shaffer and Livingood<sup>99</sup>. In this study, 823 patients received a total of 18,286 injections of bismarsen. Of these patients, 299 had latent and seroresistant syphilis, 151 had prenatal syphilis, 57 had late cutaneous or osseous involvement, 117 were in the early stages of the disease, 101 had cardiovascular involvement and 98 had syphilis of the central nervous system. Bismarsen was administered whenever possible twice a week and in uninterrupted courses of sixty injections or more.

The drug was found to be relatively nontoxic and easily administered. Although it was frequently used to treat patients who had shown untoward reactions to other arsenicals, the incidence of local and systemic reactions was low, only 5 cases of dermatitis and 5 of purpura having been observed. There were no fatalities.

In cases of early syphilis, bismarsen brought about healing, although more slowly than did other arsenicals. The spirocheticidal action was also more gradual. It was shown to be effective in preventing progression, relapse and late complications. In cases of latent syphilis, reversal of serologic reactions was accomplished and progression of the disease prevented. With cardiovascular, late congenital and benign late forms of syphilis, favorable results were attained. The action of bismarsen was considered too slow for the treatment of active interstitial keratitis. In cases of neurosyphilis the drug is useful only for patients for whom fever and other forms of chemotherapy are contraindicated.

*New Arsonic Acids*—Several new arsonic acids, derived from naphthalene and biphenyl, have been prepared by Doak and his co-workers<sup>100</sup> in order that their spirocheticidal activity might be investigated. The arsonic acids have been reduced to the corresponding arsine oxides.

*Mapharsen*—Fractional dose therapy of experimental trypanosomiasis has shown the trypanocidal action of mapharsen *in vivo* to be of relatively short duration. Yet arsenic can be recovered from the blood and tissues of the experimental

98 Beerman, H., Pariser, H., and Gordon, J. H. Further Observations on Trisodarsen for the Treatment of Syphilis, *Am J Syph, Gonorr & Ven Dis* **26** 670 (Nov) 1942.

99 Beerman, H., Shaffer, B., and Livingood, C. S. Bismarsen (Bismuth Arsphenamine Sulfonate) for the Treatment of Syphilis, *J A M A* **120** 333 (Oct 3) 1942.

100 Doak, G. O., Eagle, H., and Steinman, H. G. Arsine Oxides of Naphthalene and Biphenyl, *J Am Chem Soc* **64** 1064 (May) 1942.



animal for relatively long periods after injections of mapharsen Wright and Peters<sup>101</sup> have studied experimentally the apparent lack of parallelism between these two facts

The procedure consisted in determining the minimum trypanocidal concentration of the blood arsenic of rats at various intervals after intravenous injection of the maximum tolerated dose of mapharsen and comparing this with the minimum trypanocidal concentration of the uninjected drug Following the injection of mapharsen, the trypanocidal activity of the blood was exceedingly high for one-half to one hour, but decreased steadily thereafter and disappeared completely after twenty-four to thirty-six hours Blood arsenic levels dropped slowly but became somewhat higher as arsenic was returned to the blood stream from the tissues Since this returning arsenic is nontypanocidal and since the incubation of mapharsen with blood produces a much slower decrease in activity than that occurring in vivo, it appears that the tissues play a major role in inactivation of the drug

Despite the fact that the present day treatment of syphilis calls for repeated administration of subcurative doses of arsenical drugs in alternate courses with bismuth, most studies of the curative effects of antisyphilitic drugs in experimental animals have been made on the basis of the injection of a single completely curative dose To ascertain the therapeutic effects of subcurative doses, Swinyard, Hirschfelder and Wright<sup>102</sup> have studied the results of serial administration of various subcurative doses of mapharsen in the treatment of *T. equiperdum* infections in rats

From the standpoint of the effect of dosage, there appeared to be a comparatively sharp break in the efficiency of doses smaller than 50 per cent of the minimal curative dose Doses in excess of this were uniformly curative in two or more doses at all time intervals, even at intervals of ninety-six hours, apparently because the initial dose destroyed a sufficiently large number of the organisms that the infection could not be restored to its former level by the time the next injection was given

At dosages below 50 per cent of the minimal curative dose, the results were much more dependent on the time interval between injections With smaller doses, the duration of the curative efficiency of a single injection of mapharsen in the rat did not exceed twelve hours

The authors' results indicate

that the duration of the trypanocidal action of mapharsen is sufficiently short that maximum clinical benefit cannot be expected to be obtained from the injection of the drug at weekly or even semi-weekly time intervals Maximum therapeutic results from the clinical use of mapharsen appear to be indicated by the administration of repeated subcurative doses of the drug at a time interval sufficiently short that a constantly spirocheticidal concentration of the drug will be maintained in the blood stream night and day for a period of time sufficiently long to produce a high percentage of "permanent cures" in a single course of treatment The time interval elapsing between injections should apparently not exceed 12 hours The dosage should be the maximum that the incidence of clinical toxicity will permit The injection of dosages that are too small, even though injected at frequent intervals, may be comparatively wasteful therapeutically from failure to achieve the necessary minimal curative blood level of the arsenic compound, yet potentially dangerous from the standpoint of the production of toxic manifestations

101 Wright, H N, and Peters, L Trypanocidal Activity and Arsenic Content of Rat Blood Following Intravenous Administration of Mapharsen, *Proc Soc Exper Biol & Med* **52** 3 (Jan) 1943

102 Swinyard, E A, Hirschfelder, A D, and Wright, H N The Therapeutic Effects of Repeated Subcurative Doses of Mapharsen on *T. Equiperdum* Infections in the Rat *J Pharmacol & Exper Therap* **75** 367 (July) 1942



Trivalent arsenicals of the arsphenamine series are poorly absorbed from the gastrointestinal tract and have little therapeutic activity when administered by mouth. This is largely due to the fact that arsphenamines behave somewhat as colloids, and arsphenamine itself is largely insoluble at the  $p_H$  of the body fluids.

Because mapharsen is soluble and freely dialyzable at neutrality, Rosenthal<sup>103</sup> has tested its therapeutic efficacy orally against *T. equiperdum* infections in mice. Since it was anticipated that the arsenoxides would cause local irritation of the gastrointestinal tract, further experiments were conducted in which glutathione was added to the mapharsen solution prior to administration.

Thus administered orally, mapharsen was found to possess curative action against *T. equiperdum* infections in mice. The addition of 2 mols of glutathione decreased toxicity without affecting therapeutic activity.

*Effectiveness of Arsenicals Against Bacteria*—Osgood and his co-workers<sup>104</sup> have determined in cultures of living human marrow cells the comparative effectiveness of several arsenical and sulfonamide drugs against various species of bacteria. Clinically and in experimentation on animals, variables such as the size of the inoculum, the number and strain of organisms present, the natural resistance of the host and the presence of antibodies are difficult to control. By using cultures of human marrow, these variables can be controlled, quantitative studies thus being made more reliable.

In marrow cultures, arsenic trioxide and seven pentavalent organic arsenicals tested were ineffectual against all the species of bacteria studied. Six trivalent arsenicals (neoarsphenamine, arsphenamine, sulfarsphenamine, trisodarsen, mapharsen and phenarsine hydrochloride), in concentrations corresponding to about 100 micrograms of arsenic per hundred cubic centimeters, were effective against six species of bacteria: *Staphylococcus aureus*, *Streptococcus viridans* (groups A and B), *Streptococcus haemolyticus*, *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae* and *Haemophilus influenzae*. They were ineffective against *Diplococcus pneumoniae*, *Escherichia coli*, *Eberthella typhosa*, *Salmonella schottmuelleri*, *Streptococcus viridans* (group C) and *Streptococcus anhaemolyticus*.

*"Sulfonamide Effect" of Sodium Arsanilate*—Paraaminobenzoic acid is an essential growth factor required for the multiplication of many different bacteria. The efficacy of the sulfonamide group of drugs has been explained by their structural similarity to paraaminobenzoic acid and their ability to displace this essential metabolite. Hirsch<sup>105</sup> points out that other substances, devoid of sulfonamide groups, may have a similar action. He notes that sodium arsanilate (sodium salt of paraaminobenzene arsenic acid) reduces the speed of bacterial growth against *Bacillus coli* and that the antibacterial effect of the drug can be inhibited by paraaminobenzoic acid.

*Detoxication of Arsenicals with Paraaminobenzoic Acid*—Sandground and Hamilton<sup>106</sup> find that paraaminobenzoic acid is highly effective in reducing

103 Rosenthal, S. M. The Trypanocidal Action of 3-Amino-4-Hydroxyphenyl Arsenious Oxide ("Mapharsen") Administered Orally with Glutathione, *J. Pharmacol. & Exper. Therap.* **76** 358 (Dec.) 1942.

104 Osgood, E. E., and others. The Comparative Effectiveness of Arsenical Compounds and Sulfonamide Drugs Against Bacterial Infections, *J. Lab. & Clin. Med.* **28** 953 (May) 1943.

105 Hirsch, J. The "Sulfanilamide Effect" of Substances Devoid of Sulfo Groups, *Science* **96** 139 (Aug. 7) 1942.

106 Sandground, J. H., and Hamilton, C. R. Studies on the Detoxication of Organic Arsenical Compounds. I. Detoxication by Means of p-Aminobenzoic Acid of Certain Pentavalent Arsenical Drugs Given in Massive Doses to Rats, *J. Pharmacol. & Exper. Therap.* **78** 109 (June) 1943.

fatalities among rats to which acutely poisonous doses of carbarsone, acetarsone, tryparsamide, arsanilic acid and phenylarsonic acid have been administered. This detoxication is independent of the route by which either the phenylarsonic compound or the paraaminobenzoic acid is given. There was, however, no inhibition by paraaminobenzoic acid of the trypanocidal action of these pentavalent arsenical drugs.

The same authors<sup>107</sup> found it difficult to determine what quantitative relationship exists between the minimal amount of paraaminobenzoate required to neutralize the action of any specified quantity of pentavalent arsenical. By the administration of sufficient paraaminobenzoate, practically all rats were protected against a dose of pentavalent arsenicals sufficient to kill all the animals. It was found that 15 mg per kilogram of paraaminobenzoate was sufficient to protect 50 per cent of the rats and to prolong the survival time of a group of rats receiving 400 mg per kilogram of arsanilic acid.

Continuing the study, Sandground<sup>108</sup> found that the time factor entering into the sequence of administering uniform doses of paraaminobenzoate and either of two typical phenylarsonic acid derivatives to rats is sufficient to influence the survival rate of the group. Injection of paraaminobenzoate up to three hours before the administration of the arsenical confers protection on nearly all animals. In contrast, the injection of the arsenical thirty minutes before the giving of the paraaminobenzoate is associated with a reduction in the group protection, and this reduction is in direct proportion to the increase in the time interval.

*Similarity of Bismuth Preparations*—According to Clausen and his co-workers,<sup>109</sup> there exists a striking qualitative and quantitative similarity of toxicities and limits of tolerance as well as of antisypilitic efficacy among the various bismuth preparations when they are administered intravenously. When they are given intramuscularly, the spirocheticidal activity does not differ significantly from that following intravenous administration, although the tolerance of the host is markedly increased.

The similarity of the maximal tolerated dose and the therapeutic indexes of the compounds tested when given intravenously, in contrast to their marked differences when given intramuscularly, indicates that the difference in rate of absorption from intramuscular deposits is the most important factor in accounting for any variation which occurs.

The therapeutic efficacy of a bismuth compound, as well as its toxicity, is in direct proportion to its content of elemental bismuth. The similarity of the minimal curative dose of any bismuth preparation administered either intravenously or intramuscularly and the similarity in the toxicity of preparations given intravenously suggest that basically all bismuth compounds ultimately act in a common form rather than in the form in which they were injected.

*Determinations of Blood Bismuth*—Studies of the pharmacology of bismuth compounds have not in the past included determinations of bismuth levels in the blood, which have been estimated from bismuth excreted in the urine.

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107 Sandground, J. H., and Hamilton, C. R. Studies on the Detoxication of Arsenical Compounds. II. Correlation of the Quantity of p-Aminobenzoic Acid Required to Protect Rats Against High Doses of Carbarsone and Arsanilic Acid, *J. Pharmacol. & Exper. Therap.* **78** 203 (June) 1943.

108 Sandground, J. H. Studies on the Detoxication of Arsenical Compounds. III. The Time Factor Influencing p-Aminobenzoate Protection of Rats Receiving Lethal Doses of Phenyl Arsonates, *J. Pharmacol. & Exper. Therap.* **78** 209 (June) 1943.

109 Clausen, N. M., Longley, B. J., Green, R. E., and Tatum, A. L. A Study of the Similarities of Several Representative Types of Bismuth Preparations Used in the Therapy of Experimental Syphilis, *J. Pharmacol. & Exper. Therap.* **76** 338 (Dec.) 1942.

Delp, Walker and Sondern<sup>110</sup> have succeeded in making determinations of blood bismuth on 7 syphilitic patients receiving a water-soluble bismuth compound (potassium bismuth saccharate). Values of 3 to 5 micrograms were obtained promptly after the intramuscular injection of this preparation. Cumulative effects were evident with multiple injections, and values of 5 to 7 micrograms were easily maintained. After cessation of therapy there was evidently a rapid fall in blood bismuth levels, but minimal amounts of the metal were found for a considerable time.

*Bismuth Melanosis and Female Sex Hormones*—Sulman and his co-workers<sup>111</sup> found that when female albino rats were simultaneously treated with organic bismuth compounds (bismuth phenylethylacetate, bismuth butylthiolaurate, bismuth chinolate and bismuth adipinate) and estrogens or chorionic gonadotropin, bismuth melanosis of the vagina developed in 30 to 80 per cent of the animals. The reaction seemed to be conditioned by hyperemia of the vagina from the action of the hormones. Bismuth melanosis in sexual organs other than the vagina was seldom observed, and the rest of the body was always found free of impregnation with bismuth. In male rats simultaneously treated with a bismuth compound and testosterone propionate, bismuth melanosis of the genital tract occurred only occasionally.

*Iodine in Saliva*—Bruger and Member<sup>112</sup> have found marked increases in the concentration of iodine in the saliva following the oral administration of potassium iodide, iodine dissolved in poppyseed oil and ethyl diiodobromide. The maximal concentration of salivary iodine occurred approximately one to two and a half hours after the ingestion of potassium iodide.

#### TREATMENT

*Bismuth Compound for Latent Syphilis*—Kahn and Becker<sup>113</sup> report the results of treatment of 200 patients with late latent syphilis with "large amounts of bismuth combined with a moderate amount of an arsenical," comparing them with the results obtained by the Cooperative Clinical Group. The scheme of therapy used was as follows: one course of ten injections of a bismuth compound, three courses of combined bismuth and arsenical treatment, after each of which was interposed one month's rest and a course of eight injections of a bismuth compound, another rest period, and finally three long courses of bismuth therapy separated by six months and one year. Total therapy amounted to twenty-four doses of an arsenical and eighty-six of a bismuth compound. For this type of treatment, the authors claim an advantage over the shorter, alternate course scheme of therapy used by the Cooperative Clinical Group, who obtained maximum results with twenty injections of an arsenical and less bismuth than was used by the authors.

The data presented, however, do not support the authors' premise, since the material has been analyzed with insufficient regard for the statistical concepts involved. The two groups of patients are not strictly comparable. In the first

110 Delp, M. H., Walker, N., and Sondern, C. W. Blood Bismuth Studies. Preliminary Report of Syphilitic Patients Treated with a Water-Soluble Preparation, *Am J Syph, Gonorr & Ven Dis* **27** 193 (March) 1943.

111 Sulman, F., Levy-Hochman, S., and Tietz, H. G. Selective Bismuth Melanosis of the Female Genital Tract Induced by Treatment with Sex Hormones, *Endocrinology* **32** 293 (March) 1943.

112 Bruger, M., and Member, S. On the Excretion of Iodine in the Saliva, *Am J Physiol* **139** 212 (June) 1943.

113 Kahn, D., and Becker, S. W. The Use of Bismuth Compounds in Syphilotherapy. II. The Results of Treatment of Latent Syphilis by Bismuth Compounds Combined in Part with Arsenicals, *J A M A* **120** 338 (Oct 3) 1942.

place, it is necessary to realize that of the patients in the Cooperative Clinical Group series who received prolonged treatment, many were so treated because of need for further therapy. In the present study, prolonged treatment was given routinely. In addition, the previous treatment which the patients in the present group received was disregarded, despite the fact that 30 per cent had received such therapy. Moreover, all of the patients in the present group had syphilis in the later stage of latency, whereas 30 per cent of the Cooperative Clinical Group series had early latent infection.

The higher proportion of satisfactory results in the authors' series is more apparent than real. The percentage of patients with clinical progression, the true test of therapy of late latent syphilis, is smaller in their group among patients under observation up to ten years, but among those observed more than ten years a smaller percentage of the Cooperative Clinical Group's series had progressed. For an unexplained reason, none of the patients in the authors' group had died, and none was "under treatment, doing well." A readjustment of the rates in the Cooperative Clinical Group's series in consideration of these facts improves the comparative results, bringing the observed differences within the range of chance variation.

There is no satisfactory proof that the prolongation of therapy with additional courses of bismuth improves the prognosis for patients with late latent syphilis. There is, on the other hand, reason to believe that the prevention of clinical progression can be effected satisfactorily by considerable less treatment than that indicated by Kahn and Becker.

*Thiamine Hydrochloride for Lightning Pains*—Cochems and Kemp<sup>114</sup> treated 26 patients with typical tabetic lightning pains with thiamine hydrochloride given intravenously. The average number of injections was eighteen, with an average dose of 61 mg, over a period averaging eight months. Analysis of the results reveals that 17 patients (65 per cent) experienced no ultimate relief of pain, 4 (16 per cent) apparently obtained partial relief, and 5 (19 per cent) apparently obtained complete relief. Definite proof was lacking that improvement in any instance was due to thiamine because the observation period was insufficiently long for the exclusion of spontaneous remission and psychic effect. The authors conclude that intravenous injections of thiamine hydrochloride are valueless in the alleviation of tabetic lightning pains in the majority of cases and of doubtful value in the remainder.

*Vitamin Therapy*—None of the manifestations of syphilis respond dramatically to vitamin therapy. Moreover, there is no satisfactory evidence that any of the vitamins significantly decrease the toxicity of the arsenical drugs. O'Leary<sup>115</sup> notes that although thiamine has been used as supplementary therapy for tabes dorsalis, lightning pains, visceral crises, atrophy of the optic nerve and interstitial keratitis and as an adjunct to tryparsamide treatment, though ascorbic acid has been used to prevent arsenical dermatitis and though riboflavin has been employed for interstitial keratitis, all have been found to have insignificant value.

#### UNTOWARD EFFECTS OF TREATMENT

*Mortality Data*—For the past seventeen years, medical officers of the Navy have been required to submit reports of the number of doses of arsenicals administered and detailed information regarding any toxic reaction therefrom.

114 Cochems, K. D., and Kemp, J. E. Intravenous Thiamin Chloride (Vitamin B<sub>1</sub>) in the Treatment of Tabetic Lightning Pains, *Am J Syph, Gonorr & Ven Dis* 26: 574 (Sept) 1942.

115 O'Leary, P. A. Vitamin Therapy in Dermatology and Syphilology, *Arch Dermat & Syph* 46: 628 (Nov) 1942.

The most recent data thus obtained have been compiled by Stephenson, Chambers and Anderson<sup>116</sup> In the period 1925 to 1941, 1,792,383 injections of various arsenicals have been given, with 52 fatal reactions, a ratio of 1 death to every 34,469 injections Fifty of the 52 deaths were due to neoarsphenamine, 1 to arsphenamine and 1 to mapharsen A total of 288,585 injections of mapharsen have been given The one fatality following this drug occurred twenty-four hours after the first injection Postmortem observations included cerebral edema and hemorrhage Of 881 reactions from all arsenicals recorded, 353 were ascribed to vasomotor phenomena and 336 to arsenical dermatitis

*Arsenical Encephalopathy*—The severe and usually fatal cerebral manifestations due to the toxic effects of arsenicals are most commonly referred to as "hemorrhagic encephalitis," although other terms have been used, such as cerebral purpura, serous apoplexy, medullary perivascular necrosis and pericapillary encephalorrhagia

Two instances of arsenical encephalopathy following neoarsphenamine are reported by Tuta and Stagman,<sup>117</sup> who believe that a relationship exists between the relatively mild vasomotor or nitritoid crises and the progressive vascular changes leading to cerebral edema followed by hemorrhagic infiltrations The most common clinical findings in the latter condition are headache, vomiting, rapid development of unconsciousness, convulsions and fever These symptoms usually appear two or three days after the first, second or third injection of an arsenical drug Occasionally, however, the symptoms may be delayed, and at times many injections may precede the onset The majority of patients die within four days after the appearance of the reaction

The authors' conception of the pathogenesis of arsenical encephalopathy is as follows

Vasodilatation with increased capillary permeability is followed by stasis and exudation of fluid from the terminal blood vessels causing a cerebral edema Instances have been reported where the cerebral edema has been a predominant feature and only a few or no hemorrhages were found Later, red blood cells escape from the walls of the capillaries and vessels of precapillary dimensions, resulting in the picture of a hemorrhagic encephalitis with clinical symptoms, particularly of stupor or coma

As Halcrow<sup>118</sup> points out, the causal factor in arsenical encephalopathy is unknown, but it seems to be unrelated to the arsenic radical, since poisoning with inorganic arsenic compounds does not give rise to such cerebral symptoms The authors think it unlikely that overdosage is at fault, since in most recorded cases symptoms have occurred after the second or third injection However, in view of the greatly increased frequency of the reaction during and after the intensive arsenotherapy of early syphilis, dosage is surely incriminated It is not in the nature of a Herxheimer reaction since cerebral complications have followed arsenical therapy in nonsyphilitic patients As symptoms occur early in the course of therapy, it is possible that an allergic factor exists There is evidence of a toxic action of the drugs on capillaries

Attention is drawn to the need for early recognition of the condition, since therapy seems unavailing unless instituted soon after the onset

116 Stephenson, C S, Chambers, W M, and Anderson, L T (a) Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1941, U S Nav M Bull 40 1015 (Nov) 1942, (b) Toxic Effects of Arsenical Compounds as Employed in the Treatment of Disease in the United States Navy, 1941, *ibid* 41 259 (Jan) 1943

117 Tuta, J A, and Stagman, J Encephalopathy Following Neoarsphenamine, Am J Clin Path 12 387 (July) 1942

118 Halcrow, J P A Case of Haemorrhagic Encephalopathy Following Arsenical Therapy, Brit M J 1 663 (May 29) 1943

Having observed 4 patients with arsenical encephalopathy, 3 of whom were pregnant women, Nelson and his co-workers<sup>119</sup> believe the condition to be more frequent than usually is stated. In 3 instances hemorrhagic encephalitis occurred about the tenth day after treatment was begun with sodium arsphenamine or mapharside. All the reactions occurred in the winter season, at a time when vitamin intake is relatively low. It is impossible to determine in advance which patient will have this complication, but the authors' experience suggests that a pregnant woman should be regarded as a "potential reactor."

Courville and Marsh,<sup>120</sup> who have studied 12 cases of postarsphenamine encephalopathy, describe multiple symmetric foci of hemorrhagic necrosis as part of the pathologic picture of this condition. According to these authors, the lesion is closely allied to pericapillary encephalorrhagia, in that it is composed of many perivascular ring hemorrhages. There was a tendency for these hemorrhagic foci to localize in regions of both gray and white matter of the brain. The corpus callosum, the optic thalamus, the external capsule and the frontal and parieto-occipital centricums were the sites of predilection. There was also a tendency for the lesion to occur in symmetric areas of the brain.

From the data presented, it is apparent that multiple symmetric foci of hemorrhagic necrosis, together with the disseminated petechial hemorrhages and possible gross cerebral hemorrhage, constitute the essential pathologic changes in the clinical syndrome of postarsphenamine hemorrhagic encephalopathy.

In Thomas, Wexler and Dattner's<sup>121</sup> series of 764 patients treated for early syphilis with massive dosages of mapharsen, there were 8 patients with symptomatic cerebral reactions, 2 of whom died. In their experience, arsenical reactions of this type vary as to time of onset in relation to treatment and as to duration of symptoms. The significant observation is recorded that in patients with cerebral reactions there is usually a marked increase in protein in the cerebrospinal fluid. This is usually but not necessarily associated with pleocytosis.

Because of the authors' fear of cerebral reactions, the spinal fluid was examined before and after intensive treatment in 250 cases of early syphilis. The spinal fluid was also examined whenever "secondary" fever or unusual symptoms indicated it. In the course of these examinations, 8 patients were found who had marked abnormalities of the spinal fluid but no symptoms. It is believed that these alterations may portend serious trouble and that their finding calls for interruption of therapy.

*Arsenical Myelopathy*—Arsenical intoxication may produce pathologic changes in an organ in two ways—by direct action on the parenchyma and by affecting its nutrition through involvement of the nutrient blood vessels. In the brain, the lesions of arsenical toxicity usually are of the vascular type, producing the classic picture of "hemorrhagic encephalitis."

Lichtenstein<sup>122</sup> notes that, in contrast to the changes in the brain, the changes in the spinal cord following therapy with the arsenicals usually results from damage to the parenchyma. Histologic alterations of postarsphenamine myelitis

119 Nelson, R. B., McGibbon, C., and Glyn-Hughes, F. Arsenical Encephalopathy—A Complication Occurring During the Treatment of Syphilis, *Brit. M. J.* **1**: 661 (May 29) 1943.

120 Courville, C. B., and Marsh, C. Cerebral Lesions Following Administration of Neoarsphenamine. Multiple Symmetric Foci of Hemorrhagic Necrosis of the Brain, *Arch. Dermat. & Syph.* **46**: 512 (Oct.) 1942.

121 Thomas, E. W., Wexler, G., and Dattner, B. Cerebral Reactions Associated with Massive Mapharsen Treatment of Early Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**: 529 (Sept.) 1942.

122 Lichtenstein, B. W. Acute and Subacute Toxic Myelopathies Following Therapy with Arsphenamine, *Arch. Neurol. & Psychiat.* **48**: 740 (Nov.) 1942.

include degeneration of the ganglion cells and the myelin of the nerve fibers, with proliferative changes in the astroglia, malacia, necrosis, and inflammatory phenomena, such as perivascular and leptomeningeal cellular infiltrations

As a rule, postarsphenamine myelopathy is located in the lower thoracic and the lumbar portion of the spinal cord, although the parenchymatous alterations may extend upward into the brain stem. Degeneration of the peripheral nerves not infrequently is associated with the lesions of the cord. The disorder usually is acute or subacute in course, with death resulting from respiratory paralysis or sepsis. In nonfatal cases there is evidence of permanent damage to the spinal cord.

*The Bone Marrow During Intensive Arsenotherapy*—Studying the sternal bone marrow of 14 patients during intensive arsenotherapy (five day intravenous drip), Schwind<sup>123</sup> found no significant effect of the treatment on either the erythrocytic or the leukocytic series of cells. Three of the patients had a shift to the left in the Schilling index of the peripheral blood, although the total leukocyte count was within normal limits. These patients had a corresponding increase in neutrophilic band forms and metamyelocytes in the bone marrow. The other 11 had normal peripheral blood pictures, and the differential counts of their marrows were within the range of normal.

*Histamine Treatment of Exfoliative Dermatitis*—Encouraging results from the use of histamine therapy in certain allergic conditions led Jenkins<sup>124</sup> to study this drug in the treatment of postarsenical dermatitis. The author believes that histamine therapy hastens recovery in this condition, since in his hands more satisfactory results were obtained than with any other type of treatment. His series of cases is small, and the interpretation of the results is complicated by the fact that some had received routine therapy with colloidal baths, ephedrine and phenobarbital. Moreover, the results were appraised on the basis of duration of hospitalization, an end point subject to considerable discretionary bias. The findings are suggestive, but further clinical trial with histamine is necessary to evaluate the proper place of this form of therapy in the treatment of exfoliative dermatitis caused by the arsenical drugs.

*Sodium Thiosulfate Treatment of Exfoliative Dermatitis*—Abramowitz and his co-workers<sup>125</sup> report the results of treatment with sodium thiosulfate of 5 patients with arsenical dermatitis, of 1 with dermatitis due to bismuth and of 1 with dermatitis due to gold. All patients were put on a restricted diet, usually bananas and milk. Determinations of arsenic in the urine were made, and freshly prepared sodium thiosulfate was administered intravenously. The authors conclude

1 Using as a criterion the twenty-four hour output of arsenic, we have been unable to demonstrate that sodium thiosulfate in the doses commonly employed increases the urinary excretion or alleviates dermatitis due to the arsphenamines. It is therefore of little diagnostic or therapeutic value.

2 Although our experimental evidence is limited, it would appear that sodium thiosulfate is without effect on urinary excretion of bismuth or on dermatoses subsequent to alternate bismuth and arsenic therapy. In 1 case the urinary excretion of gold also was not affected by sodium thiosulfate.

123 Schwind, J. L. The Bone Marrow in the Five Day Treatment of Syphilis, *Proc. Soc. Exper. Biol. & Med.* **52** 128 (Feb.) 1942.

124 Jenkins, E. C. Treatment of Postarsenical Dermatitis with Histamine, *Ven. Dis. Inform.* **24** 11 (Jan.) 1943.

125 Abramowitz, E. W., Mattice, M. R., and Botvinick, I. Doubtful Value of Sodium Thiosulfate in Therapy of Arsenical Dermatitis, *Arch. Dermat. & Syph.* **47** 175 (Feb.) 1943.



*Postarsphenamine Jaundice*—In a twelve month study of icterus in the Canadian Army, Mitchell <sup>126</sup> compares the incidence of catarrhal jaundice with the occurrence of jaundice following arsenotherapy of syphilis

The incidence of clinical jaundice among those receiving arsenotherapy for syphilis was 36.5 times as high as in those who were not so treated. The drug used for about 90 per cent of the men was neoarsphenamine. Jaundice was three times as frequent in this group as in the smaller group treated with mapharsen. It is suggested, although without documentation, that there is a large number of cases of infectious hepatitis without jaundice and that it is the association of two hepatotoxic agents, the arsenic and the toxic agent of infectious hepatitis, which produces a higher incidence of infectious hepatitis in patients under arsenotherapy.

*Respiratory Allergy to Arsenicals*—Cutaneous hypersensitivity to the arsenical drugs used in the treatment of syphilis is not unusual. Respiratory hypersensitivity, however, is sufficiently rare as to warrant single case reports. Saunders <sup>127</sup> reports an instance of such allergy, in which sneezing, rhinorrhea and asthma followed the inhalation of mapharsen, arsphenamine or neoarsphenamine. Similar symptoms followed the making of patch tests or scratch tests with these same drugs.

*Erythema of the Ninth Day*—Gresser and Thomas <sup>128</sup> report that superficial punctate keratitis may occur in association with fever and a generalized erythema of the skin as part of the clinical entity known as Milian's erythema of the ninth day. The complication occurred in 2 syphilitic patients and in a patient with Vincent's infection after treatment with trivalent arsenicals. The immediate complaints consisted of smoky or blurred vision, accompanied by redness of the eyes, photophobia, lachrimation and a mild sensation of sandiness or of a foreign body. These symptoms either followed the height of the erythema or occurred as the erythema faded and desquamated. The acute stage persisted from two to four weeks. The punctate lesions, which by slit lamp examination appeared to be edematous cells rather than erosions, tended to appear in crops at five to six day intervals, the new lesions appearing before resolution of the old, and affected mainly the central corneal area. In all cases the keratitis was self limited, being uninfluenced in evolution by therapy.

*Bismuth Stomatitis*—Ronchese <sup>129</sup> reports favorable results from the use of hexametaphosphate and talc in the form of a tooth powder in the treatment of bismuth stomatitis.

*Bismuth Anuria*—The toxic effects of bismuth on the kidney ordinarily are benign. However, Witkowski <sup>130</sup> reports 2 cases of severe renal damage in infants under treatment with bismuth for congenital syphilis. In 1 anuria and death followed the administration of ten injections of sodium bismuth thioglycollate.

Stitt <sup>131</sup> reports severe renal damage following a single dose of sodium bismuth thioglycollate to an infant, and cautions that care should be exercised in administering bismuth, especially to infants.

126 Mitchell, H. S. The Incidence of Catarrhal Jaundice Compared with Jaundice Following Arsenotherapy of Syphilis, *Canad. M. A. J.* **48**:94 (Feb.) 1943.

127 Saunders, T. S. Respiratory Allergy from the Arsphenamines, *J. Allergy* **14**:76 (Nov.) 1942.

128 Gresser, E. B., and Thomas, E. W. Superficial Punctate Keratitis in Milian's Erythema of the Ninth Day, *Arch. Ophth.* **28**:245 (Aug.) 1942.

129 Ronchese, F. Bismuth Stomatitis, *Urol. & Cutan. Rev.* **46**:462 (July) 1942.

130 Witkowski, J. L. Toxic Effects with Anuria Resulting from Bismuth Injections in the Treatment of Congenital Syphilis in Infants, *Urol. & Cutan. Rev.* **46**:770 (Dec.) 1942.

131 Stitt, P. G. Bismuth Poisoning. Toxic Effects with Anuria Resulting from a Single Injection of a Bismuth Preparation, *Urol. & Cutan. Rev.* **46**:780 (Dec.) 1942.



*Embolia Cutis Bismuthica*—Arterial embolism following the injection of bismuth is a rare untoward reaction to antisyphilitic treatment. Reporting a case of embolia cutis bismuthica, Goldschlag<sup>132</sup> suggests that even the most careful technic may fail to prevent the accident. A small amount of bismuth may be deposited in the wall of an artery and subsequently rupture into the lumen. To prevent the accident the author advises that needles of relatively wide gage be used, that after aspiration the needle be detached and that injection be made into a muscle which is relaxed.

*Bismuth Hepatitis*—When jaundice complicates the treatment of a patient with syphilis, the complication is usually attributed to intercurrent infection, to the administration of arsenicals or possibly to hepatorecurrence of syphilis. Kulchar and Reynolds<sup>133</sup> stress the importance of bismuth as a cause of hepatitis and report 121 cases in which the heavy metal appeared to be implicated.

In treating 1,032 inmates of San Quentin prison, the authors observed 121 who became jaundiced while bismuth was being given. Treatment had been with iodo-bismutol with saligenin for 82 of the 121 patients. Only 4 patients became icteric when the initial course of therapy was with bismuth. The remaining 117 had received arsenicals in some form prior to the course of bismuth therapy during which hepatitis occurred. The onset of jaundice was noted within four weeks of the last injection of an arsenical drug in 34 patients, but evidence of hepatic damage did not appear until four or more weekly injections of bismuth had been given in 83, and not until after eight or more weekly injections in 56.

Treatment was subsequently continued in 107 of the cases. In 9 there was a recurrence of the jaundice. This occurred during bismuth therapy in 4, while arsphenamine was given in another 4, and during treatment with trypanisamide in 1.

The authors believe that the effect of previously administered arsenicals as well as factors of diet, alcoholism and intercurrent infection all predispose the liver to damage from bismuth and that bismuth hepatitis is a summation effect resulting from the interaction of several factors which individually are insufficient to cause the clinical manifestations of hepatitis, with bismuth the precipitating factor. The occurrence of signs or symptoms suggestive of toxic hepatitis during antisyphilitic therapy is a relatively frequent and perplexing problem. Kulchar and Reynolds outline a fairly convincing brief to indict bismuth, but their data lend themselves also to conclusions favoring arsenical causation in many of the cases presented. Most syphilotherapists, while admitting that bismuth may precipitate toxic hepatitis in a patient with preexisting damage of the liver, question the frequency with which it does so.

#### EARLY SYPHILIS

*Dark Field Study*—Branch<sup>134</sup> stresses certain pertinent observations on the diagnosis of early syphilis by dark field microscopy: (1) that clinical examination alone is unsatisfactory, since a positive result of dark field examination not infrequently is found in lesions lacking the classic features of induration, painlessness and inguinal lymphadenopathy, (2) that spirochetes other than *S. pallida* frequently are found in penile lesions, in some cases associated with the organism of

<sup>132</sup> Goldschlag, F. *Embolia Cutis Bismuthica. An Untoward Accident Following the Intramuscular Administration of Bismuth Subsalicylate in Oil*, M. J. Australia **2** 144 (Aug 22) 1942.

<sup>133</sup> Kulchar, G. V., and Reynolds, W. J. *Bismuth Hepatitis. A Survey of One Hundred and Twenty-One Cases*, J. A. M. A. **120** 343 (Oct 3) 1942.

<sup>134</sup> Branch, A. *Darkfield Examination of Penile Lesions*, Canad. M. A. J. **48** 55 (Jan) 1943.

syphilis, and (3) that a single negative result of dark field examination does not rule out syphilis. Many experienced physicians do not concur in the author's recommendation of the delayed dark field examination as a practical procedure. Since the accurate identification of *S. pallida* requires observation of the organism in its motile state, and since motility rapidly is lost with the passage of time outside the body, the delayed procedure is far from being entirely satisfactory for the definitive diagnosis of syphilis.

In the diagnosis of secondary syphilis, many physicians rely on the clinical characteristics of the eruption plus a positive serologic reaction, examination for *S. pallida* by dark field microscopy being used only when moist papules (condylomas) are present. The feasibility of examining serum from other cutaneous lesions under the dark field microscope is championed by Agee,<sup>135</sup> whose case reports indicate that the procedure is practical for routine use in the clinic. The advantages of the method are that the finding of *S. pallida* definitely establishes the diagnosis and that treatment may be started without waiting for the report of the serologic test.

*Newer Concepts of Reinfection*—Schoch and Alexander<sup>136</sup> point out that in patients with early syphilis treated with intensive arsenotherapy reinfection may be relatively frequent. According to their published reports, earlier workers with intensive treatment methods, recognizing the extreme difficulty of differentiating reinfection from infectious relapse, have leaned to the side of conservatism and have classified all such conditions as relapse, and therefore as indicating failure of treatment. However, the clinical evidence in favor of reinfection in many patients given intensive arsenotherapy is at least as strong as the evidence for heretofore accepted examples of reinfection in patients treated by standard methods.

Ten cases of reinfection are recorded. Dark field observations, quantitative reagin titer curves and epidemiologic data were used to support clinical observations and impressions. It is highly desirable to make the differentiation between infectious relapse and reinfection in patients treated by intensive methods, since only thus can the results of such therapy be evaluated properly.

Many attempts have been made to set up suitable criteria for differentiating infectious relapse of syphilis from reinfection. Such criteria have not been entirely satisfactory. The widespread use of intensive arsenotherapy has reopened the question and reemphasized the importance of the problem, since the criteria for patients receiving "standard" treatment are not suitable for intensively treated patients. Shaffer<sup>137</sup> reviews the criteria which have been proposed, suggesting the following for patients given intensive treatment:

- 1 Accuracy of the original diagnosis of syphilis assumed on the basis of the administration of intensive treatment by organized hospital or clinic
- 2 Patient has remained seronegative or has progressed to that state
- 3 Spinal fluid examination negative prior to second infection (This is desirable but not essential)
- 4 A lesion, clinically acceptable as a chancre, develops at a site different from the first
- 5 Patient is seronegative but darkfield positive at time of second infection
- 6 Definite exposure history for second infection (Ideally, source of second infection should be identified)

135 Agee, O. F. The Use of the Darkfield Microscope for Diagnosis of Generalized Secondary Lesions of Syphilis, *New Orleans M. & S. J.* **95** 329 (Jan.) 1943

136 Schoch, A. G., and Alexander, L. J. Reinfection in Syphilis. Newer Concept of Reinfection Encountered with Ten-Day Arsenotherapy of Early Syphilis Controlled by Quantitative Serologic Tests, *Am. J. Syph., Gonorr. & Ven. Dis.* **27**:15 (Jan.) 1943

137 Shaffer, L. W. Criteria of Reinfection in Syphilis, *Ven. Dis. Inform.* **24** 113 (April) 1943

7 If seropositive at time of supposed second infection, patient should be held in isolation without treatment until after the proper interval, at which time secondaries develop to establish validity

8 Seropositive cases of clinically acceptable primary lesions or cases presenting characteristic secondary manifestations with a history or remains of a chancre may be classified as probably reinfection, if they fulfill the above criteria

Supposed reinfections occurring within 6 months after intensive treatment is completed cannot be differentiated from potential superinfections, cases occurring at a later date may be assumed to be reinfections

#### INTENSIVE THERAPY

*Intensive Arsenotherapy*—Evaluating the present status of intensive arsenotherapy, Shaffer<sup>138</sup> states

Intensive methods of treatment must still be considered experimental. The potential hazard, at least of short intensive courses, makes it necessary to advise that they should not be attempted by physicians without extensive experience in the treatment of syphilis. Further information is being rapidly accumulated, and it is expected that such experience will permit the establishment of a definite procedure to be recommended in the near future for use in private practice and in the military services. Intensive therapy is being tried in various types of latent and late syphilis, but its use in such cases is highly experimental and not as yet recommended. Its use should be restricted to previously untreated cases of early (primary and secondary) syphilis.

Among the efforts to compress the treatment of syphilis into a period shorter than the "standard" eighteen months is the twenty week schedule studied by Hood<sup>139</sup>. Concomitant weekly injections of mapharsen and of a bismuth compound were given to 134 patients with early syphilis, of whom only 66 successfully completed the course of twenty weeks' treatment.

Under this schedule of treatment, 94.4 per cent of all primary and secondary lesions involuted completely within six weeks, and seronegativity was achieved by 90.9 per cent of the patients. No correlation was found between the initial reagin titer and the time required to reach seronegativity. Unsatisfactory results (seroresistance, serorelapse, clinical relapse and involvement of the central nervous system) are recorded for 13.6 per cent of the patients. The author believes that his results compare not unfavorably with the results of treatment with other arsenical drugs and other schedules of therapy.

Yeager and Connolly<sup>140</sup> have treated 103 patients with early syphilis by giving twenty injections of mapharsen (totaling 960 to 1,200 mg. of the drug) over a period of thirty days. In 2 of the patients toxic encephalopathy developed, and 1 died. The number of therapeutic "failures" was 9.7 per cent.

Schoch and Alexander<sup>141</sup> have treated 350 patients by intensive arsenotherapy. Of these, 208 were treated by the ten day syringe method (120 mg. of mapharsen per day for ten days) and 142 were given "smaller individual doses over a longer period of time". In the entire group, they encountered hemorrhagic encephalitis 3 times, with 1 death. One hundred and three patients treated by the ten day syringe method have been under observation from six to eighteen months. In this group, 77 per cent attained clinical and serologic "cure". The results in 11

138 Shaffer, L. W. Present Status of the Intensive Arsenotherapy of Early Syphilis, *Ven Dis Inform* **24** 108 (April) 1943.

139 Hood, B. J. The Results of a Twenty Week Treatment Schedule for Early Syphilis, *Am J Syph, Gonorr & Ven Dis* **27** 267 (May) 1943.

140 Yeager, F. W., and Connolly, S. M. Short Term Intensive Arsenotherapy of Early Syphilis, *Tri-State M J* **15** 2858 (Dec.) 1942.

141 Schoch, A. G., and Alexander, L. J. Intensive Arsenotherapy of Early Syphilis Follow-Up Report on the Ten Day Syringe Method of Treatment, *Arch Dermat & Syph* **46** 128 (July) 1942.

per cent are pending. In the remaining 12 per cent the treatment was a failure (3 patients with infectious relapses, 1 with periostitis, 6 with serologic relapses, and 2 with positive reactions of the cerebrospinal fluid). The authors state that "These results compare favorably with those of the 5 day continuous intravenous drip method."

Since the German invasion of Norway in April 1940, a large portion of the Norwegian Merchant Navy has been isolated from its bases but remains actively engaged in prosecution of the war. Because of the acute need for the services of the naval personnel and because of a serious increase in syphilis in this group, intensive arsenotherapy has been administered. Kvittingen<sup>142</sup> reports favorable results of therapy in 100 men treated by daily injections of mapharside. The first 82 patients received 760 mg of the drug within five days, the remaining 18 received 1,000 mg in the same period. Only 1 serious reaction is recorded, toxic encephalopathy associated with morbilliform dermatitis. Follow-up results are for obvious reasons, difficult. It is felt that, despite the increased risk of treatment, in a time of emergency the procedure is justifiable.

Once a soldier is hospitalized for primary syphilis, he is not returned to duty until the lesion is healed. It is important, therefore to effect healing as rapidly as possible in order that the man may return to his duties and training. Pelzman and Greenwald<sup>143</sup> believe that by giving daily injections of mapharsen at the start of treatment the average number of noneffective days can be substantially reduced. Neoarsphenamine, because of its higher toxicity, cannot be employed in this manner.

*Arsenotherapy Combined with Fever*—Thomas and Wexler<sup>144</sup> have administered 280 courses of intensive treatment with mapharsen alone and 549 with mapharsen combined with fever induced by typhoid vaccine. Injections of mapharsen were given twice daily (0.1 Gm twice a day for six days). Three plans of combining fever with mapharsen were used: (1) total of 0.54 Gm of mapharsen and four fever treatments in nine days; (2) total of 0.84 Gm of mapharsen and two fever treatments in nine days; and (3) total of 0.7 Gm of mapharsen and three fever treatments in seven days.

The reactions encountered with the multiple injection method were not appreciably different from, nor more frequent than, those reported with the intravenous drip method. The use of typhoid vaccine increased the discomfort of treatment but was not in itself dangerous. Two deaths are recorded (one in each of the two main treatment groups), both attributable to toxic encephalopathy.

The therapeutic results may be summarized as follows:

Treatment	Patients	Probably Favorable	Unfavorable
(1) Mapharsen (0.9-1.2 Gm)	151	83.78%	16.22%
(2) Mapharsen (0.66-0.84 Gm)	122	74.99%	25.01%
(3) Mapharsen (0.54-0.6 Gm) plus 4 sessions of fever	128	86.46%	13.54%
(4) Mapharsen (0.7-0.84 Gm) plus 2 or 3 sessions of fever	171	85.49%	14.51%

<sup>142</sup> Kvittingen, J. Syphilis Treated with Daily Multiple Injections of Mapharside, *Brit M J* **1** 69 (Jan 16) 1943.

<sup>143</sup> Pelzman, I. A., and Greenwald, R. Preliminary Intensive Treatment of Primary Syphilis by Daily Injections of Arsenicals, *Am J Syph, Gonorr & Ven Dis* **26**:627 (Sept) 1942.

<sup>144</sup> Thomas, E. W., and Wexler, G. Rapid Treatment of Early Syphilis. Report of Two Hundred and Eighty Treatment Courses with Mapharsen Alone and Five Hundred and Forty-Nine Courses with Mapharsen Combined with Fever, *Arch Dermat & Syph* **47** 553 (April) 1943.

The authors believe that their results, both with mapharsen alone (total dose 1 Gm or more) and with a combination of fever induced with typhoid vaccine and less than 0.9 Gm of mapharsen, compare favorably with the results of prolonged continuous routine treatment. The therapeutic results obtained with less than 1 Gm of mapharsen alone are definitely less satisfactory than when a total dose of 1 Gm or more is used. The risk of arsenical encephalopathy increases with the amount of mapharsen given. The combination of fever induced by typhoid vaccine with massive mapharsen therapy does not prevent cerebral reactions, but it lessens the frequency of their occurrence by permitting a smaller total dose of mapharsen without loss of therapeutic effectiveness.

Coutts<sup>145</sup> has treated 13 patients with early syphilis by the use of artificial fever together with a single intravenous injection of arsenoxide and one intramuscular injection of bismuth. All responded favorably to this treatment except 1, a woman, two and a half months pregnant, who had an infectious relapse three months after the one day treatment. Two serious although not fatal reactions are recorded. One patient had hepatitis, and another had anemia with azotemia.

An attempt has been made by Simpson and his co-workers<sup>146</sup> to determine on an experimental basis the value and limitations of a quantitative serologic test for syphilis in relation to clinical response in patients with early syphilis who were subjected to artificial fever therapy alone. It was the original plan of this experiment to treat 25 patients with clinically obvious primary and secondary syphilis with approximately fifty hours of fever with a temperature between 105 and 106 F. Fever was administered in sessions of five hours' duration at weekly intervals for ten weeks. After the first 8 patients were treated by this method it became obvious that fever therapy alone would not cure early syphilis. It was therefore deemed advisable to abandon this type of treatment because of clinical relapses. However, the following observations were made. The primary or secondary lesions tended to heal after the first few fever treatments, but as this type of treatment progressed, the serologic reactions of the blood for syphilis became more strongly positive. In every instance the progressive rise in titer preceded a clinical relapse.

The same group of workers<sup>147</sup> have studied the serologic response to treatment with combined fever and chemotherapy. Twenty-seven patients with primary or secondary syphilis were treated with combined fever and chemotherapy. The fever was given either in twelve sessions of three hours or in ten sessions of five hours, with temperature levels of 105 to 106 F. The fever was administered once or twice a week. During the course of each fever treatment, patients were given either 0.3 Gm of neoarsphenamine, or 40 mg of mapharsen along with 0.2 Gm of metallic bismuth. A few patients in the group received bismarsen. After the termination of fever treatment, chemotherapy was continued for an additional twenty weeks. All patients in the series were followed for at least four years, the longest period of observation being eight years.

The 27 patients were divided into three groups. The first group comprised 5 male patients with primary syphilis treated twice weekly. In this group all patients

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145 Coutts, W. E. Consideraciones sobre algunos aspectos de venereologia contemporanea, *Bol. Ofic. san. panam.* **21** 1175 (Dec.) 1942.

146 Simpson, W. M., Rose, D. L., and Kendell, H. W. Quantitative Serologic Studies in Early Syphilis. I. Treatment with Artificial Fever Alone, *Ven. Dis. Inform.* **23** 403 (Nov.) 1942.

147 Kendell, H. W., Rose, D. L., and Simpson, W. M. Quantitative Serologic Studies in Early Syphilis. II. Treatment with Artificial Fever Combined with Chemotherapy, *Ven. Dis. Inform.* **23** 408 (Nov.) 1942.

had a reversal to negative of the serologic reaction for syphilis within twenty-three to sixty-four days. Those patients with the highest original titers tended to take the longest time to attain negative serologic reactions. In this group no patient had clinical or serologic relapses.

The second group was comprised of 10 patients, 5 males and 5 females, who had secondary syphilis and who received treatment once a week. Three of these patients had received from one to five injections of an arsenical preparation prior to combined fever and chemotherapy. The titers of all of these patients tended to be somewhat higher than those of the first group, and it took fifty to ninety-three days after treatment was begun to attain negative serologic reactions. Again, those patients with the highest titers had more slow reversal. There were no clinical or serologic relapses in the group.

The third group was composed of 12 persons, 10 males and 2 females, all with secondary syphilis, treated with combined fever and chemotherapy twice a week. Seven of these had received from one to twelve intravenous injections of an arsenical prior to starting fever therapy. The time at which serologic negativity was attained varied between twenty-eight and sixty-six days after treatment was begun. As in the other two groups, without exception, low serum titers tended to reverse more quickly than high serum titers.

Taking the three groups as a whole, no correlation could be observed between the height of the initial serologic titer and the clinical status of the patient. Patients having clinically comparable lesions exhibited great variations in the initial titers. When treatment was adequate, the decline in the serologic titer progressed at a constant rate. There was no appreciable difference in the rate of serologic reversal whether patients received treatment weekly or more intensively, twice weekly.

Since the results obtained by these prolonged courses of combined fever and chemotherapy were so encouraging, the Dayton group sought to compress the duration of treatment into a still shorter period. Twenty-three patients<sup>148</sup> with dark field-positive primary syphilis and strongly positive serologic reactions were subjected to a single ten hour session of artificial fever with a temperature of 106 F, combined with 0.25 Gm of bismuth subsalicylate in oil, and mapharsen in a total dose varying between 120 and 240 mg. Two patients were given 240 mg by the continuous intravenous drip method. This procedure was abandoned in favor of the administration of the drug by the syringe method. In the latter case, the drug was given in 60 mg doses at intervals of three hours, from two to four such doses were administered.

The only complication noted to this combined therapy was the development of transient jaundice. Serologic reactions of the blood for syphilis reversed to negative in twenty-one to one hundred and seventy-six days. There was no correlation between the amount of drug given and the rapidity with which the reactions become negative. The progressive decline of titer to negativity was essentially the same as that noted in persons receiving a larger total amount of both artificial fever and chemotherapy over a longer period. Patients in this group have been followed for six months, during which there have been no serologic relapses.

The cautious statements made by the Dayton workers in these papers regarding the very small series of patients treated by them formed the basis for the outrageously sensational *Reader's Digest* article by de Kluif, "Found—A One Day Cure for Syphilis," commented on unfavorably in the previous review of this

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148 Rose, D. L., Simpson, W. M., and Kendell, H. W. Quantitative Serologic Studies in Early Syphilis. III. Treatment with a Single Intensive Session of Combined Fever-Chemotherapy, *Ven. Dis. Inform.* **23**: 411 (Nov.) 1942.

series<sup>1</sup> Physicians, if not the public, will once more be impressed by the conservatism of science and the recklessness of sensational medical journalism

An editorial writer,<sup>149</sup> commenting on a recent popular article on the so-called "one day cure" for syphilis by combined arsenic-fever therapy, writes

The method has very definite hazards Not everyone can tolerate a fever of 106° F, and patients with certain defects should never be exposed to such a temperature Too few cases have been treated and too short a time has elapsed to know if there are any late serious effects of the treatment and if the results of the disease are permanent It may be a step forward in the treatment of syphilis, but much experimental work must be done to be sure that this particular technic is the proper procedure for every case of syphilis

Physicians can assure their questioning patients that the one-day treatment is in the experimental stage and is not a safe and sure procedure and that it will eventually be made readily available if scientific evidence warrants its acceptance

*Experimental Evaluation of Intensive Methods of Therapy*—In the evaluation of a new drug or a new therapeutic procedure, it is customary to determine toxicity and therapeutic efficacy in the experimental animal prior to clinical trial However, intensive arsenotherapy of early syphilis has been extensively used without benefit of such experimental data

A large scale laboratory study by Eagle and Hogan has clarified the situation These investigators have studied twelve different mapharsen treatment schedules in which the total duration of treatment varied from ten seconds to six weeks, and in which the frequency of injection varied from standard clinic practice of weekly injections to injections repeated four times daily

In their first paper, Eagle and Hogan<sup>150</sup> describe the effect on toxicity of mapharsen of varying the method of administration, the frequency of injections and the total duration of treatment Judged by toxicity in rabbits, the continuous intravenous drip offered no significant advantages over multiple injections On any schedule of injections, whether weekly, triweekly, daily, several times daily or a continuous intravenous drip, the total amount of mapharsen tolerated can be increased by prolongation of the period of treatment It is possible, further, to increase the amount of mapharsen which can be given with safety within a given time period by increasing the frequency of injections Although less drug can be given per injection, the total tolerated dose is thereby significantly increased

Various methods have recently been suggested for the intensification of anti-syphilitic treatment The decision as to the optimum treatment schedule would be clearly facilitated by a systematic study of the "chemotherapeutic index" (the margin of safety between the amount of drug tolerated and the amount found to be therapeutically effective) as it is affected by varying the frequency of injections and the total duration of treatment In their second paper Eagle and Hogan<sup>151</sup> present data on the therapeutic activity of mapharsen in experimental rabbit syphilis and on the toxicity-activity ratio (margin of safety) as they are affected by the method of administration The authors' summary is as follows

1 The total curative dose of mapharsen in syphilitic rabbits (CD<sub>50</sub>) was

- (a) 6.3 gm per kg for a single injection, and 8.1 mg per kg for 6 weekly injections,
- (b) 7.7 mg per kg for 12 triweekly injections (4 weeks),

<sup>149</sup> The One-Day Cure for Syphilis, editorial, New England J Med **227** 720 (Nov 5) 1942

<sup>150</sup> Eagle, H, and Hogan, R B An Experimental Evaluation of Intensive Methods for the Treatment of Early Syphilis I Toxicity and Excretion, Ven Dis Inform **24** 33 (Feb) 1943

<sup>151</sup> Eagle, H, and Hogan, R B An Experimental Evaluation of Intensive Methods for the Treatment of Early Syphilis II Therapeutic Efficacy and Margin of Safety, Ven Dis Inform **24** 69 (March) 1943



(c) 63, 30, and 64 mg per kg for daily injections repeated for 1, 4, and 12 days respectively,

(d) 59, 62, and 36 mg per kg for multiple injections daily continued for 1, 2, and 4 days respectively, and

(e) 89, 68, and 112 mg per kg for an intravenous drip (5 and 6 hours daily) continued for 1, 2, and 4 days respectively

The dose which cured 50 per cent of the animals in the various schedules was 35 to 75 per cent of the corresponding minimal curative dose

2 The intravenous drip was significantly less effective than multiple syringe injections administered over the same time period

3 Comparing the 8 treatment schedules involving syringe injections repeated at varying intervals (2 hours to 1 week), and continued for varying periods (10 seconds to 6 weeks), the curative dose of mapharsen was largely unaffected by the method of administration, varying only between 30 and 81 mg per kg. With reservations necessary because of the large experimental error, there was some indication that syringe injections completed in 4 days were more effective than either longer or more intensified schedules. Excluding the two schedules completed within 4 days, the curative dose on the remaining 6 schedules varied only between 59 and 81 mg per kg

4 On any schedule of injections, whether weekly, triweekly, daily, multiple daily, or intravenous drip, any desired margin of safety between the toxic and therapeutic dose of mapharsen could be obtained by appropriate prolongation of the treatment period. The intensification of treatment by arbitrarily decreasing the number of injections, and giving more mapharsen per dose, necessarily resulted in a closer approach to the toxic level, and a narrowed margin of safety

5 The short-term intravenous drip (1, 2, or 4 days) usually gave an even lower margin of safety (21, 47, and 40 respectively) than did multiple daily syringe injections over the same time period (21, 43 and 106 respectively). This is due to the fact that the intravenous drip was only slightly less toxic, and was usually less effective than schedules involving multiple syringe injections. The margins of safety cited are only a fraction as great as those which could be obtained by prolonged daily, triweekly, or weekly injections

6 By properly adjusting the total number of injections, the duration of treatment on weekly injections can be cut 50 to 65 per cent *without reducing the margin of safety* by injecting mapharsen triweekly instead of weekly, and can be reduced to an even greater extent by giving injections daily or several times daily. The intravenous drip does not permit a maximal safe condensation of treatment. It is less effective in this respect than daily injections, and only slightly more effective than a triweekly schedule. This is due primarily to its low therapeutic efficacy

7 An appreciable condensation of treatment beyond that permitted by triweekly, daily, or multiple daily injections can be accomplished only at the cost of safety, by an arbitrary decrease in the total number of injections. Necessarily, more mapharsen must then be given at each injection, with a closer approach to the toxic level, and a proportionate decrease in the margin of safety

The clinical implications of the experimental study are also discussed by Eagle and Hogan<sup>152</sup>. It is pointed out that in the various intensive treatment schedules which have been used for the treatment of early syphilis in man, the "curative" dose of mapharsen is largely independent of the frequency of injections or the duration of therapy. The curative dose has been 20 to 30 mg per kilogram, or approximately 1,500 mg for a man weighing 60 Kg. The margin of safety provided by any intensive therapeutic procedure is therefore primarily a function of its toxicity. The administration of 1,200 mg of mapharsen by intravenous drip in five days, with a safety factor of 30, has resulted in a mortality of 1/200, weekly injection, with a safety factor of 10, has a mortality of less than 1/3,000, and treatment schedules with intermediary factors of safety have resulted in a correspondingly intermediate incidence of deaths

<sup>152</sup> Eagle, H., and Hogan, R. B. An Experimental Evaluation of Intensive Methods for the Treatment of Early Syphilis. III. Clinical Implications, Ven Dis Inform **24** 159 (June) 1943



To keep the mortality rate from antisyphilitic treatment less than 1/1,000 it is estimated that a margin of safety of 6 to 8 is required. Any treatment schedule completed in twenty days or less will result in a mortality rate in excess of this. The desired margin of safety is provided, however, by giving the total curative dose in thrice weekly injections for seven to twelve weeks, daily injections for approximately six weeks, or multiple daily injections or an intravenous drip for an estimated period of four to six weeks. Treatment thrice weekly provides almost the maximum condensation of treatment consistent with safety and convenience. It has the advantage of permitting the therapy to be carried out on an ambulant basis. This method is now under study in eighty cooperating clinics.

Kolmer and Rule<sup>153</sup> have determined the toxicity of mapharsen and of neoarsphenamine administered by the intravenous drip method to normal rabbits as compared with the toxicity of these drugs when given by multiple injection. The maximum tolerated dose of mapharsen for rabbits with the continuous intravenous drip method (daily for five days) was about 0.06 Gm per kilogram of weight, with the syringe method, the single maximum tolerated dose was about 0.015 Gm per kilogram. The maximum tolerated dose of neoarsphenamine given by five day intravenous drip was about 0.3 Gm per kilogram, and with the syringe method of administration the single maximum tolerated dose was about 0.225 Gm per kilogram. The tolerance of rabbits for both compounds appeared better with the continuous intravenous drip method than with the administration of single doses by syringe injection, this being particularly notable in the case of mapharsen.

The arsenic content of the blood of patients with early syphilis treated intensively with multiple injections of mapharsen has been determined by Siegel and his co-workers<sup>154</sup>. Characteristic and essentially similar curves were recorded for 15 patients who received mapharsen alone and 16 patients who received fever therapy with typhoid vaccine in addition to mapharsen. The mean morning values of blood arsenic of patients receiving mapharsen alone showed a progressive rise to 16 micrograms of arsenic per hundred cubic centimeters of whole blood in the course of the first five days of therapy. The mean morning values of blood arsenic of patients who received combined mapharsen and fever therapy showed a prompt rise to about 10 micrograms per hundred cubic centimeters after one day of treatment, remaining essentially unchanged during the next three days and climbed during the next three days to 17 micrograms.

Comparison of these results from the multiple syringe method with the results of observations with the continuous intravenous drip method reveals a close parallelism in morning low point concentrations of blood arsenic obtained with the two methods of administration.

*Intensive Arsenotherapy via the Bone Marrow*—Following the demonstration of the feasibility of introducing fluids into the body by way of the bone marrow when veins are inaccessible, as in infants and obese adults, Wile and Schamberg<sup>155</sup> have investigated the possibility of intensive arsenotherapy by this route. Seven rabbits were given massive arsenotherapy by bone marrow infusion drip, 4 mg of mapharsen per kilogram of body weight each day for five successive days. To

153 Kolmer, J. A., and Rule, A. M. Mapharsen and Neoarsphenamine Administered by Continuous Intravenous Drip Method. Toxicity for Rabbits, Arch. Dermat. & Syph. **47** 665 (May) 1943.

154 Siegel, J., Goldstein, D. H., and Goldwater, L. J. Intensive Treatment of Syphilis with Multiple Injections of Mapharsen. Concentration of Arsenic in the Blood, Arch. Dermat. & Syph. **46** 783 (Dec.) 1942.

155 Wile, U. J., and Schamberg, I. L. Pulmonary Fat Embolism Following Infusions via the Bone Marrow, J. Invest. Dermat. **5** 173 (Aug.) 1942.

2 control rabbits intravenous massive arsenotherapy was administered. Pulmonary fat emboli, presumable from displacement of fat from the bone marrow, were demonstrated in 5 of the 7 rabbits treated via the bone marrow, whereas no fat emboli were seen in the 2 animals treated by vein. Except for fat embolism, the visceral histologic damage seen in rabbits treated by bone marrow infusion was essentially the same as that noted in rabbits treated by vein. The toxicity of mapharsen did not appear to be altered when administered by the former route. The finding of pulmonary fat emboli in animals treated by bone marrow infusion leads the authors to conclude that the procedure "cannot at present be considered free from hazard in human beings."

*Intensive Arsenotherapy in Pregnancy*—Rattner<sup>156</sup> has treated 27 pregnant syphilitic women by five day massive dose arsenotherapy, usually with the concurrent administration of bismuth. The treatment was well tolerated by both mother and fetus regardless of the stage of the pregnancy or the duration of the syphilitic infection. In no case was there a severe reaction or interference with the pregnancy. Of the 27 patients, 1 was lost from observation, 25 gave birth to full term, nonsyphilitic infants, and 1 syphilitic infant was born to a mother who may have acquired a second infection following therapy for the first. In addition to this group, 5 other patients who had been treated intensively subsequently became pregnant and delivered normal children although further antisyphilitic therapy was withheld.

*Intensive Arsenotherapy in Congenital Syphilis*—Demonstration of the fact that acquired syphilis in adults can be cured in five days by intensive arsenotherapy has led to the application of this form of therapy to the treatment of congenital and acquired syphilis in infants and children.

Levin and his co-workers<sup>157</sup> have treated 32 infants and children with congenital syphilis and 4 children with early acquired syphilis with massive doses of mapharsen given intravenously over periods of five days. The results of therapy in the group of patients with congenital syphilis were notably inferior to those obtained by similar treatment of early acquired syphilis in adults, and the authors believe that "the spirochetosis of congenital syphilis produces widespread changes more resistant to treatment than acquired syphilis." Of 32 patients with congenital syphilis (12 under 3½ months of age), the serologic reactions of only 12 became negative. In contrast to this, the reactions of all 4 children with early acquired syphilis promptly became negative. Quantitative serologic studies were made in all cases, and a rising titer six months after treatment was considered an indication for a second course of therapy.

The authors properly stress the importance of adequate pediatric care. All of their patients had been examined and had demonstrated their ability to take food and maintain fluid balance before being subjected to the rigorous five day treatment. There were no serious toxic reactions or deaths.

#### LATE SYPHILIS

*Latent Syphilis*—In studying latent syphilis among patients in general hospitals, Gelperin<sup>158</sup> has sought to obtain information by the questionnaire method as to

156 Rattner, H. Treatment of Syphilis in Pregnancy by the Five-Day Massive Dose Method, *Proc Inst Med Chicago* **14** 420 (May 15) 1943.

157 Levin, I. M., Hoffman, S. J., Koransky, D. S., Richter, I. B., and Gumbiner, B. Congenital and Acquired Syphilis in Infants and Children. Treatment with Massive Doses of Arsenic Intravenously, *J A M A* **120** 1373 (Dec 26) 1942.

158 Gelperin, A. The Problem of Latent Syphilis in the General Hospital, *Am J Syph, Gonorr & Ven Dis* **27** 290 (May) 1943.

(1) the extent of the problem, (2) facilities for follow-up of patients with latent syphilis, (3) whether routine serologic tests are performed, and (4) the percentage of admissions which were free

Information was obtained from 56 hospitals. Of these, 49 had follow-up services to insure posthospital treatment for patients with early syphilis, next frequent was follow-up for patients with active late manifestations of the disease, and least frequent, similar service for those with latent syphilis. Since it is the last group in whom disastrous late complications develop, a hospital that cares for the indigent sick must begin its attack with the diagnosis of latent syphilis as frequently as possible. The provision of opportunity for antisyphilitic treatment subsequent to the patients' discharge from the hospital is a responsibility shared by the hospital and the local health authority.

*Syphilis of the Eye*—A thorough review of the ocular lesions in congenital and in acquired syphilis has been published by Woods.<sup>159</sup> This splendid article, a summary of the entire subject of ocular syphilis, does not lend itself to condensation. Involvement of each of the various structures of the eye is discussed in detail. For a readable and well documented review, the original article should be consulted.

*Primary Atrophy of the Optic Nerve*—An evaluation of the results of treatment in 250 cases of syphilitic primary atrophy of the optic nerve followed over many years is detailed by Moore and his co-workers.<sup>160</sup> In their study, primary atrophy of the optic nerve was found to occur in at least 8 per cent of all patients with clinical evidence of acquired neurosyphilis. The incubation period of the condition varied widely, although the majority of patients had onset of symptoms during the second decade of the disease. Atrophy of the optic nerve occurred more than twice as frequently in tabes as in other types of neurosyphilis. In uncomplicated dementia paralytica it was found to be rare.

The therapeutic results were subjected to statistical analysis by the life table method. Among untreated patients, blindness occurred in 28 per cent within one year of onset of symptoms and in 50 per cent within two years, and less than 90 per cent were blind in twelve years. Routine antisyphilitic treatment with trivalent arsenicals and bismuth failed to alter significantly the spontaneous course of the untreated disease. Subdural therapy precipitated blindness in almost 10 per cent of patients. The slight difference between the untreated group and the group receiving subdural therapy could have been due to selection. Of patients given malaria therapy, only 9 per cent were blind at one year after onset of symptoms, 14 per cent were blind at two years, and thereafter, for observation periods up to fifteen years, no additional blindness ensued. In general, the prognosis was less favorable in the presence of central or paracentral scotomas. The authors conclude:

1 Syphilitic primary optic atrophy occurs more frequently in association with tabes dorsalis, though it not infrequently may constitute together with pupillary changes, the only clinical evidence of neurosyphilis. It is probable that the fundamental process is the same in all types of neurosyphilis.

2 The course of the untreated disease is extremely variable. The process almost always becomes bilateral soon after onset of symptoms and 90 per cent of untreated patients are blind within twelve years. There is a small group of patients in whom progression is quite slow.

159 Woods, A. C. Syphilis of the Eye, *Am J Syph, Gonorr & Ven Dis* **27** 133 (March) 1943.

160 Moore, J. E., Hahn, R. D., Woods, A. C., and Sloan, L. The Treatment of Syphilitic Primary Optic Atrophy, *Am J Syph, Gonorr & Ven Dis* **26** 407 (July) 1942.

3 Our data suggest that the development of syphilitic primary optic atrophy can be prevented by the adequate routine treatment of early syphilis

4 Routine therapy with the trivalent arsenicals and bismuth is not of any value in the treatment of syphilitic primary optic atrophy

5 Subdural treatment by the Swift-Ellis technique should be abandoned. Its dubious value in an occasional patient is outweighed by a risk of sudden extinguishment of vision in about 10 per cent of those treated

6 Fever therapy (in our hands malaria, since we have had no experience with the use of mechanically induced fever in this condition) is the only efficacious method of treatment. If visual failure progresses in spite of fever therapy, no other form of therapy is likely to be of value. It must be emphasized that these conclusions are subject to specific limitations imposed by the material upon which this study is based. Since malaria therapy was, by and large, not given to patients with the most rapidly progressive type of disease, no statement is permissible as to its efficacy in this group. It is certain that many of our untreated and routinely treated patients would not have been benefited by any treatment, indeed in many there was literally no time for treatment. The fact remains that where there is time for treatment, malaria is of definite practical value. Since early diagnosis is often possible only by routine determination of the visual fields, fundi, and visual acuity, this procedure is recommended as a routine supplement to the clinical and laboratory examinations in all patients with neurosyphilis. Only by early diagnosis and the immediate induction of malaria is there any hope of arresting the most fulminating cases

*Optochiasmatic Arachnoiditis*—When defects of the visual field occur in a patient with syphilis, they most often indicate parenchymatous disease of the optic nerve which ultimately terminates in atrophy. The possibility of adhesions about the nerves and chiasm nevertheless exists. Syphilis is an etiologic factor in optochiasmatic arachnoiditis, but there are other causes. Ryan<sup>161</sup> reports 3 cases of this condition in which syphilis was excluded as the cause. Tumor of the pituitary gland, hereditary atrophy of the optic nerve (Leber's disease) and glioma of the optic chiasm most frequently enter into the differential diagnosis

*Osseous Lesions*—The diagnosis of osseous lesions associated with acquired syphilis from the viewpoint of the radiologist is discussed by Truog<sup>162</sup>. Nine cases are detailed and the roentgenograms reproduced. In his experience, the osseous lesions of acquired syphilis may simulate many other conditions involving bone. However, the simulation is not complete, since certain characteristic changes of these other conditions are not present. Unfortunately, no information is presented as to the duration of the syphilitic infection in any of the cases. The age of certain of the patients and the destructive nature of the osseous lesions suggest that some of the infections may have been recently acquired. With the author's suggestion that "All syphilitic bone lesions should be referred to as syphilitic osteomyelitis," there should be considerable disagreement. Periostitis and osteoperiostitis not only occur but are indeed the more frequent manifestations of osseous syphilis

*Syphilis of the Larynx*—Wood<sup>163</sup> notes that in the larynx syphilitic lesions do not follow the classic time relationships of the secondary and tertiary periods. Laryngeal involvement may occur with the development of the chancre, and tertiary lesions may accompany or closely follow the secondary stage of the disease

Early laryngitis is a diffuse serous erythema, with intense swelling and formation of papular thickening of the epithelium. Superficial ulcerations, comparable to mucous patches, frequently occur. Tertiary lesions are diffuse or circumscribed gummatous infiltrations, which may break down to form deeply punched-out

161 Ryan, E. R. Optochiasmatic Arachnoiditis. Report of Three Cases, Arch Ophth 29 818 (May) 1943

162 Truog, C. P. Bone Lesions in Acquired Syphilis, Radiology 40 1 (Jan) 1943

163 Wood, E. LeR. Syphilis of the Larynx, J. M. Soc. New Jersey 40 15 (Jan) 1943

ulcerations Perichondritis may follow, with necrosis and exfoliation of cartilage With healing, there may be stenosis and deformity of the larynx Other laryngeal lesions include paralysis of the vagus nerve in syphilis of the central nervous system and involvement of the recurrent laryngeal nerve from pressure due to aneurysm of the aorta

*Syphilis of the Liver* —In an extensive review dealing with cirrhosis of the liver, Ratnoff and Patek<sup>164</sup> found that of their 386 patients with cirrhosis, 62 (16 per cent) had evidence of syphilis The high incidence of syphilis among patients with cirrhosis is not readily explained No correlation between syphilis and alcoholism is present, since syphilis is found as a precursor of cirrhosis in countries where alcoholism is unimportant as a predisposing factor (e g, Syria and India) Dietary factors may be of importance, but the precise relationship to syphilitic infection is not clear

Thirty-four of the patients in the series had been treated with arsphenamine or one of its derivatives Two of these were jaundiced during the period of therapy

In a review of nonobstructive jaundice, Ottenburg and Spiegel<sup>165</sup> say

Disease of the hepatic parenchyma is due either to infections, directly or indirectly, or to chemical agents The clinical features help little in determining the etiology of a given case Neither do the new tests of hepatic function For example, the manifestations of (1) simple (or catarrhal) jaundice, of (2) jaundice following the use of cinchophen or arsphenamine and of (3) the jaundice which occasionally appears in early secondary syphilis, are similar Most forms of acute hepatic degeneration may progress to a fatal issue with the clinical and histologic characteristics of acute yellow atrophy

Among the infectious diseases known to cause nonobstructive jaundice is syphilis In about one half of the fatal cases of congenital syphilis, involvement of the liver occurs, the most characteristic anatomic picture being a diffuse interstitial hepatitis in which huge number of spirochetes are found

The occurrence of jaundice in secondary syphilis has been recognized for many years The incidence of jaundice associated with early syphilis is estimated to be between 0.37 and 1.4 per cent Acute yellow atrophy, according to Ottenberg and Spiegel (though few syphilologists would agree), develops in about 10 per cent of the cases In one reported series of such cases jaundice appeared from two to four months after the chancre If the jaundice is untreated its duration may be three weeks to three months It generally occurs with the secondary lesions but may be present with recurrent cutaneous lesions Clinically, jaundice associated with secondary syphilis cannot be distinguished from simple jaundice, and the differentiation rests on the presence of chancre or secondary lesions The jaundice clears promptly after the administration of one of the arsphenamines

The pathogenesis is disputed, but on the basis of the fairly frequent development of acute yellow atrophy the view of Herxheimer that there is a parenchymatous degeneration seems most acceptable Spirochetes could not be found in the livers of patients who died

The authors list all of the chemicals which have been reported to be hepatotoxic agents These are divided into three groups first, those causing direct injury to the hepatic parenchyma, second, those causing primary hemolysis with secondary

164 Ratnoff, O. D., and Patek, A. J., Jr. The Natural History of Laennec's Cirrhosis of the Liver, *Medicine* **21**: 207 (Sept.) 1942

165 Ottenberg, R., and Spiegel, R. The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents. Causative Agents, Pathogenesis, Interrelationships, Clinical Characteristics, *Medicine* **22**: 27 (Feb.) 1943

injury to hepatic cells, and third, those which result in idiosyncrasy, hypersusceptibility and allergic sensitivity in human beings. The arsphenamines fall into the third group.

Distinction is drawn between the early type of postarsphenamine jaundice, which appears within the first week or two after an infection, and the delayed type, which may occur as late as three to ten months after the termination of treatment. The early type is usually associated with a definite time period after the patient receives a given dose of an arsenical, and in most cases there are initial toxic symptoms immediately after the injection, such as fever, chills, gastrointestinal disturbances and toxic erythema. Erythema of the ninth day belongs to this early type. The delayed type of jaundice is more frequent, occurring in about two thirds of all of the cases. The clinical picture may vary from that of simple jaundice to that of acute yellow atrophy.

There has now been demonstrated that there are two types of jaundice following the use of arsenical drugs which can be distinguished on the basis of laboratory tests. With the more common form there are laboratory findings of hepatocellular damage. The less frequent form is characterized by changes suggestive of biliary obstruction, such as elevated values for total blood cholesterol and cholesterol ester, a high concentration of blood phosphatase, and a negative reaction in the cephalin flocculation test. In cases of this type biopsy of the liver shows thrombi in the biliary canaliculi with cholangiolitis similar to that described by Naunyn. This obstructive type is particularly seen in early jaundice or erythema of the ninth day. The point of view that jaundice is dependent on the arsphenamines is based on a number of well known facts, as stated by Ottenberg and Spiegel:

- (1) Definite anatomic syphilis of the liver is rarely associated with jaundice.
- (2) Arsphenamine jaundice is not accompanied by serologic evidence of recurrence.
- (3) Experimentally, arsphenamine does damage the liver functions and large doses can produce jaundice in dogs.
- (4) The increased incidence of jaundice is definitely paratherapeutic.
- (5) Paratherapeutic jaundice is also observed as a complication in nonsyphilitic cases.
- (6) There is occasionally concomitant occurrence of other symptoms of arsphenamine poisoning such as the characteristic dermatitis or the aplastic anemia.
- (7) Liver damage has been demonstrated in the latent period of delayed arsphenamine jaundice. A similar variable latent period has been demonstrated with other hepatotoxins, for example, chloroform.

The differential diagnosis between simple jaundice and arsphenamine jaundice is often difficult. An asymptomatic onset, or diarrhea and dermatitis are more common in arsphenamine jaundice, while abdominal pain and tenderness are more frequent in simple jaundice. The authors believe that arsphenamine is of prime importance in most cases of delayed arsphenamine jaundice. However, the occurrence of arsphenamine jaundice with the epidemics of simple jaundice indicates that in some patients the two factors may be synergistic. It must be granted that occasionally simple jaundice may develop in a patient who is receiving antisyphilitic therapy.

Jaundice from bismuth and mercury is briefly discussed. It is believed that these two drugs are hepatotoxic agents but much less frequently than the arsphenamines.

Seeking to determine the effect of syphilitic infection and of antisyphilitic therapy on hepatic function, Vallejo and his co-workers<sup>166</sup> have studied a series

<sup>166</sup> Vallejo, V. L., de la Cuesta, L., and Rodriguez, E. La prueba de althausen in sífilografía, *Rev argent de dermatosis* 26:361, 1942.

of 17 patients with the test of Althausen, one which is concerned with the glycogenic capacity of the liver after the administration of insulin and dextrose. Judging by the results of this test, antisyphilitic therapy is well tolerated by the liver. Occasionally, diminishing hepatic function can be demonstrated, and if this is progressive, as demonstrated by the Althausen test the authors believe that antisyphilitic treatment should be suspended. Most physicians who treat syphilis no doubt will consider routine tests of hepatic function impracticable in clinic or office practice, however desirable they may be for the early detection of damage to the liver.

#### CARDIOVASCULAR SYPHILIS

*Diagnosis of Aortitis*—Kampmeier, Glass and Fleming<sup>167</sup> believe that for practical purposes the clinical diagnosis of uncomplicated aortitis is impossible. This conclusion was reached after critical analysis of 33 cases of this condition found at postmortem examination, in which clinical and pathologic observations were correlated. Sixteen of the patients had no symptoms referable to the cardiovascular system. The others were found to have pathologic evidence of disease which offered a better explanation for the symptoms and signs than did uncomplicated aortitis. Furthermore, cardiovascular symptoms and signs appeared as commonly in a group of 30 syphilitic persons who presented no evidence of aortitis at necropsy as in those patients who did show such pathologic changes. The authors concede that for an occasional patient with stenosis of the coronary ostia a diagnosis of uncomplicated syphilitic aortitis may be made with reasonable certainty, but there were no instances of this in their material.

*Histologic Changes*—It has long been known that adequate antisyphilitic treatment will bring about clinical and symptomatic improvement in syphilitic aortitis. Restoration of normal structure is not to be expected, since the tissues in the wall of the aorta, once destroyed, cannot be replaced. However, as Howe<sup>168</sup> points out, arrest of the disease by adequate therapy may be correlated with improvement in the histopathologic appearance of the aorta. In a detailed study of 17 treated patients with cases of aortitis, the amount of cellular infiltration into the aortic wall was found inversely proportional to the amount of arsenical therapy received. No correlation was demonstrated between the histopathologic appearance of the aorta and the duration of the syphilitic infection, nor was there any clearcut relationship with intensity or duration of treatment with bismuth or mercury compounds. There was no apparent correlation with the amount of arteriosclerosis or fibrosis.

*Cardiovascular Syphilis and the Industrial Employee*—Discussing the importance of cardiovascular syphilis to the industrial physician, Kotte<sup>169</sup> points out that pathologic changes in the ascending aorta are common in patients with clinically latent syphilis and that the early detection of uncomplicated aortitis is exceedingly difficult. In his opinion, every patient with untreated latent syphilis should be regarded as having aortic involvement. Heavy work aggravates the disease in such a person and may be a predisposing factor in the development of aortic dilatation, aneurysm or valvular insufficiency.

167 Kampmeier, R. H., Glass, R. M., and Fleming, F. E. Uncomplicated Syphilitic Aortitis—Can It Be Diagnosed? *Ven Dis Inform* 23:254 (July) 1942.

168 Howe, E. G. The Microscopic Pathologic Appearance of the Aorta in Treated and Untreated Cases of Syphilitic Aortitis, *Am J Syph, Gonorr & Ven Dis* 27:50 (Jan) 1943.

169 Kotte, J. H. Cardiovascular Syphilis in the Active Period of Life, *Indust Med* 11:323 (July) 1942.



*Gumma of the Heart*—Spain and Johannsen<sup>170</sup> report that in the department of pathology at Bellevue Hospital there have been seen 3 examples of gumma of the heart. In 1 of the cases there was also found extensive gummatous pulmonary arteritis. Attention is called to the fact that only 17 cases of the latter disease have been reported in the literature.

Case reports and autopsy observations are presented. In all cases, electrocardiograms revealed conduction defects. In 1 case the gumma impinged on both the tricuspid and the pulmonary valve leaflets, resulting in a functional impairment of the valves. In another, the lesion invaded the posterior mitral leaflet and produced stenosis and insufficiency.

Gumma of the heart muscle was about three times as common as diffuse syphilitic myocarditis in the autopsy series of O'Daly.<sup>171</sup> Gummas of the heart may become encapsulated or calcified, or they may undergo central necrosis with weakening of the wall of the heart to produce aneurysmal dilatation. Syphilitic aneurysms of the heart may or may not be associated with aortitis.

*Syphilitic Coronary Arteritis*—Syphilitic aortitis resulting in narrowing of the mouths of the coronary arteries is occasionally encountered. Rarely does the process extend more than a few millimeters into the coronary arteries. Marked syphilitic involvement of the coronary arteries throughout a larger portion of the vessels with involvement of the media is rare. Strassmann and Goldstein<sup>172</sup> reported such a case.

A white woman aged 35 became suddenly ill with severe pain in the hypogastrium and died while on the way to the hospital. The principal change seen at autopsy was syphilitic aortitis with narrowing of the mouths of both coronary arteries. The orifice of the left artery was narrowed to a pinpoint, that of the right to a diameter of 1 mm. There was marked concentric thickening of the branches of the coronary arteries throughout their course. The changes usually seen in arteriosclerosis were not present. Striking changes were found in the anterior descending branch of the left coronary artery. A section through the artery about 2 cm from the mouth showed slight periadventitial and intense adventitial infiltration with lymphocytes and plasma cells. There was also obliterating endarteritis of the vasa vasorum of the adventitia. The most pronounced lesion was found in the media of the left coronary artery, which was completely encircled by a dense infiltrate of lymphocytes and plasma cells. A section stained for elastic tissue demonstrated this cellular infiltrate to extend from the adventitia in some places as far as the intima. In addition, there was destruction of elastic fibers, necrosis and scar tissue formation in other areas of the media. The intima showed an area of marked fibroblastic proliferation with narrowing of the lumen of the vessel.

Burch and Winsor<sup>173</sup> have reviewed the protocols of 6,225 consecutive post-mortem examinations at the Charity Hospital at New Orleans to ascertain the incidence of myocardial infarction secondary to syphilitic coronary stenosis. Three instances of this condition were found, and 9 additional cases were added from a review of the literature. A history of severe anginal pain in a middle-aged Negro with a positive serologic reaction for syphilis and no evidence of arteriosclerosis or

170 Spain, D. M., and Johannsen, M. W. Three Cases of Localized Gummatous Myocarditis, *Am Heart J* **24** 689 (Nov) 1942.

171 O'Daly, J. A. Miocarditis gomosa y aneurismas del corazon, *Rev san y asist Soc* **8** 77 (Feb) 1943.

172 Strassmann, G., and Goldstein, P. Syphilis of the Aorta and Coronary Arteries, *Arch Path* **34** 745 (Oct) 1942.

173 Burch, G. E., and Winsor, T. Syphilitic Coronary Stenosis with Myocardial Infarction, *Am Heart J* **24** 740 (Dec) 1942.



hypertension suggests the possibility of syphilitic coronary stenosis. Approximately one fifth of all patients with syphilitic aortitis have involvement of the coronary ostia. The condition is frequently associated with aortic regurgitation. The size of the heart depends on the presence of concomitant aortic regurgitation or hypertension. The mean age of patients with coronary involvement was 45 years. Both coronary ostia were involved in the majority of cases. When myocardial infarction occurs, sudden death is the rule. In all 3 cases reported by the authors, death occurred within a few hours after the coronary occlusion became manifest. Pathologically, the appearance of the myocardium is indistinguishable from that following coronary occlusion secondary to arteriosclerosis. The latter condition not infrequently is superimposed on syphilitic coronary arteritis.

A series of 103 syphilitic patients subject to paroxysmal pain in the chest has been studied by Jones and Bedford,<sup>174</sup> with special regard to the clinical characteristics of the pain and its pathogenesis. There were 80 men and 23 women, a sex ratio of 3.5 to 1. The main clinical findings were aortic regurgitation in 67 cases, dilatation of the aorta in 59, cardiac enlargement, often slight, in 83, and essential hypertension in 26. Electrocardiograms were recorded as abnormal in 57 of the 94 cases in which they were made. Seventy-six patients were subject to angina of effort, 64, to pain apart from effort. Nocturnal attacks were common and usually independent of paroxysmal dyspnea. Attacks tended to be prolonged but were relieved by nitrites. Postmortem observations in 12 cases are given. The common lesions of syphilitic angina were aortitis and aortic regurgitation, usually combined with stenosis of the coronary ostia. There was no evidence that uncomplicated aortitis might cause anginal pain.

*Syphilitic Arteritis*—Seeking to determine the frequency of syphilis of the intermediate-sized arteries, Potenza<sup>175</sup> has studied autopsy material from 43 patients with aortitis or aneurysm. In this selected group, 30 (70 per cent) had lesions of the common carotid, the superior mesenteric or the femoral artery. The carotid was involved most commonly, sometimes apparently by continuity from the aorta, and sometimes discrete from the larger vessel. In the 43 patients there were 24 instances of carotid arteritis, 16 of femoral arteritis and 10 of involvement of the superior mesenteric artery. Histologically, infiltration of round cells and destruction of elastic tissue were demonstrated in the media of the vessels, especially about the vasa vasorum.

Aneurysms of the hepatic artery are among the rarer types of vascular lesions. Malloy and Jason<sup>176</sup> note that 85 cases are now on record. In only 7 of these was syphilis the etiologic agent, whereas arteriosclerosis was the cause in 15. The three most frequently encountered symptoms and signs were abdominal pain, hemorrhage into the gastrointestinal tract or abdominal cavity and icterus. Treatment is unsatisfactory and the prognosis grave. Ligation, the only form of surgical therapy employed to date, is dangerous because it is likely to cause death from hepatic necrosis or insufficiency.

*Serologic Tests in Cardiovascular Syphilis*—Since most of the papers dealing with the incidence of the positive serologic reaction for syphilis in cardiovascular syphilis include not only cases in which the more modern technics of examination

174 Jones, E, and Bedford, D. E. Syphilitic Angina Pectoris, *Brit Heart J* 5: 107 (April) 1943.

175 Potenza, L. Sífilis de las arterias de calibre mediano, *Rev san y asist Soc* 8: 103 (Feb) 1943.

176 Malloy, H. R., and Jason, R. S. Aneurysm of the Hepatic Artery, *Am J Surg* 57: 359 (Aug) 1942.

were used, but also cases in which studies were made in years past with less sensitive tests, Beckh<sup>177</sup> reports the results of serologic tests for syphilis made on the serums of 100 patients with cardiovascular syphilis which came to autopsy between March 1, 1933 and Jan 12, 1942. During this time the Wassermann and Kahn technics were used, and they were altered at no time during the period.

Of 51 patients with uncomplicated syphilitic aortitis, 86 per cent had positive serologic reactions for syphilis. Of 49 patients with either aortic insufficiency or aneurysm, 88 per cent had positive reactions, and an additional 4 patients, which brings the total to 96 per cent, gave histories of having had either positive reactions at some time in the past or a history of antisyphilitic treatment.

*Angiocardiography*—Taylor and McGovern<sup>178</sup> have studied the hearts and aortas of 100 patients with the use of diodrast as a contrast medium for angiocardiography. Included in this group were patients with cardiovascular syphilis. Enlargement of the left ventricular chamber, muscular hypertrophy, regurgitant lesions and aneurysms of the aorta were readily demonstrated by the technic.

The injection of diodrast was controlled by preliminary determination of the circulation time. Reactions to the injections were observed in most subjects, but none was severe enough to warrant discontinuing the injection. The chief reaction was a sharp transient fall in blood pressure.

#### SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

A symposium on neurosyphilis presented by the Massachusetts Society for Research in Psychiatry<sup>179</sup> affords a review of this subject in the light of present day knowledge.

By way of introduction to the symposium, Perkins<sup>179a</sup> cites data which indicate that substantial progress has been made in making available adequate treatment for dementia paralytica. Comparing the period 1921 to 1930 inclusive with the decade 1931 to 1940, fewer patients with dementia paralytica were admitted to State hospitals, fewer deaths from this cause occurred and the number of patients discharged as improved has increased.

Solomon<sup>179b</sup> notes that "knowledge of paresis and neurosyphilis is more complete than that of any other diagnostic category in psychiatry." Nevertheless, he indicates a number of unsolved problems of diagnosis and therapy still awaiting definite answer.

The long term results of a study of the cases of 268 patients with syphilis of the central nervous system treated with diathermy are presented by Barton and his co-workers<sup>179c</sup>. Having tried several different methods of employing fever therapy, the authors believe the treatment of choice to be electromagnetic induction in a

177 Beckh, W. The Serologic Reaction in Cardiovascular Syphilis, *Am Heart J* **25**:307 (March) 1943.

178 Taylor, H. K., and McGovern, T. Evaluation of Angiocardiography, *J A M A* **121**:1270 (April 17) 1943.

179 (a) Perkins, C. T. Progress in Neurosyphilis from a State-Wide Point of View, *Dis Nerv System* **3**:261 (Sept) 1942. (b) Solomon, H. C. Present-Day Trends in the Investigation of General Paresis, *ibid* **3**:262 (Sept) 1942. (c) Barton, W. E., Borkovic, E. J., Zuker, J. M., and Malamud, I. Results of Artificial Fever Therapy in Syphilis of the Central Nervous System, *ibid* **3**:264 (Sept) 1942. (d) Kopp, I. Evaluation of the Clinical and Serologic Results in the Treatment of General Paresis by Malaria, Mechano-Therapy and Tryparsamide, *ibid* **3**:270 (Sept) 1942. (e) Freeman, W. The Relative Efficacy of Various Methods of Treating General Paresis, *ibid* **3**:302 (Sept) 1942. (f) Rose, A. S. Interpretations of the Spinal Fluid in Neurosyphilis, *ibid* **3**:280 (Sept) 1942. (g) Rothschild, D., and Sharp, M. L. Neuropathologic Features of General Paresis in Relation to Mental Disturbances, *ibid* **3**:310 (Sept) 1942.

humidified cabinet, the patient's temperature being brought to 106 F and maintained at that level for four hours for each of seven periods spaced not more frequently than every other day. The course is repeated after six months if deemed necessary. Continuous chemotherapy with tryparsamide, bismuth and mapharsen in alternate courses is given on completion of the fever treatment.

Kopp,<sup>179d</sup> on the other hand, believes a combination of fever and tryparsamide to be most effective. His results with malaria therapy are superior to those obtained with artificial fever when both are followed by prolonged chemotherapy.

Freeman<sup>179e</sup> disagrees, and says that malarial therapy combined with chemotherapy was not as effective as diathermy fever in combination with similar chemotherapy. In his experience, active specific therapy reduces the death rate from dementia paralytica regardless of the patients' age. Acute infections, especially of the respiratory tract, are the most frequent cause of death of patients with this disease.

Discussing the results of examination of the spinal fluid in cases of neurosyphilis, Rose<sup>179f</sup> says he has found that in parenchymatous syphilis of the central nervous system the spinal fluid returns to normal more slowly than in other types. Return of the spinal fluid to normal in one year or less is considered to be evidence against the diagnosis of dementia paralytica regardless of the clinical symptoms or treatment. An early return of the total protein content and the cell count to normal levels is a fair indication of a satisfactory outcome.

The relationship between neuropathologic changes and mental disturbances in 17 cases of dementia paralytica is discussed by Rothschild and Sharp.<sup>179g</sup> In 13 of these cases the severity of the clinical disturbances showed a fairly close correlation with the neuropathologic abnormalities. In 4 cases a lack of correlation was observed, and in this group personality factors seemed to play a role. It is suggested that a favorable outcome in dementia paralytica depends not only on effective antisyphilitic therapy but also on the integration of the patient's personality.

Analyzing the cases of neurosyphilis admitted to the Ontario Hospital, London, Ontario, Canada, during the five year period 1936 to 1940, McCausland and Straker<sup>180</sup> found a steady decline in the admission rate of patients with syphilis of the central nervous system. Two facts appear from the analysis: (1) Few patients admitted to a hospital for persons with mental disease previously had received adequate antisyphilitic treatment, and (2) patients who had received treatment prior to hospitalization had the best prognosis. Of the treated group, those receiving both malaria therapy and tryparsamide had the most favorable outcome.

*Syphilis of the Cerebral Veins*—Syphilitic lesions of the cerebral arteries and arterioles are not uncommon. Little attention has been given, however, to the changes in the central nervous system resulting from syphilis of the cerebral veins in the absence of appreciable arterial involvement. Marsh<sup>181</sup> states that the pathologic changes in the cerebral veins are much the same as those occurring in the arteries. Primary involvement of the veins in the absence of arterial changes is difficult to establish because impairment of venous circulation alone is rarely fatal. By the time death ensues there usually is advanced involvement of both arteries and veins. The author's case report concerns a patient with meningo-vascular neurosyphilis whose death was due to thrombosis of the superior cerebral veins.

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180 McCausland, A., and Straker, M. An Analysis of Neurosyphilis Over a Five-Year Period, *Canad. M. A. J.* **47**: 240 (Sept.) 1942.

181 Marsh, C. Thrombosis of the Superior Cerebral Veins as a Consequence of Meningo-vascular Syphilis, *Bull. Los Angeles Neurol. Soc.* **8**: 18 (March) 1943.

*Tabetic Arthropathy*—Steindler, Williams and Guri,<sup>182</sup> who have observed 134 patients with 214 Charcot joints, discuss this lesion in detail. In only 57 patients was there outspoken evidence of tabes dorsalis, and no less than 76 patients had symptoms referable to the joint as the first of which they complained. Manifestations detected by roentgen examination included osteosclerosis, fragmentation, absorption of bone, free body formation, exostoses and new bone formation, extra-articular ossification, osteoporosis, pathologic fracture, dislocation, disalignment and effusion.

In this series the knee joint was most frequently involved (50.9 per cent). For the treatment of Charcot's knee, the authors recommend a well fitted long leg brace entirely immobilizing the joint, supplied with a tuber seat arrangement to eliminate weight bearing. The operative treatment of choice in early stages is fusion rather than resection.

Charcot joints most often occur in the knee, ankle, hip and shoulder. More rarely they appear in the articulations of the vertebral column. The characteristics of the lesion when the vertebral bones are involved are discussed by Amyot, Vasquez and Genest.<sup>183</sup> This lesion is in itself painless, but it may produce pain of the radicular type by compression of the spinal nerves through the formation of osteophytes or through destruction of the intervertebral disk. All parts of the articulation may be involved in the destructive process. The authors believe that local vasodilatation with congestive stasis is a factor in the genesis of trophic osteoarthropathy.

*Orthostatic Hypotension in the Tabetic Form of Dementia Paralytica*—Orthostatic hypotension, previously reported in association with tabes dorsalis, also occurs in the tabetic form of dementia paralytica, as reported by Freeman and Robertson,<sup>184</sup> who note that the condition does not prevent administration of malarial therapy. The diagnostic features of the condition include (1) decrease in systolic and diastolic blood pressure, with vertigo, diplopia and occasionally syncope when the patient rises to the erect position, (2) generalized or localized diminution of perspiration, (3) failure of the pulse rate to increase normally after exercise or when the erect position is assumed, (4) relative recumbent diuresis, as compared with the output of urine when the patient is erect, (5) accentuation of symptoms during hot weather, (6) loss of libido and potentia, and (7) often a low basal metabolic rate, increased blood urea nitrogen and decreased excretion of phenolsulfonphthalein.

*Lissauer's Type of Dementia Paralytica*—Dementia paralytica in which focal symptoms are a predominant feature and there are circumscribed areas of atrophy in one or both cerebral hemispheres has come to be known as Lissauer's type. Various theories have been advanced to explain its pathogenesis. Some have believed the changes within the areas of atrophy were merely regions of increased reactivity to invasion by *S. pallida*. Others have thought that cerebral endarteritis contributes to the picture. Altered permeability of the cerebral vessels, "toxic" products and changes in the colloidal state of the cerebral tissues have also been advanced to explain this unusual type of syphilitic process. The studies of Galbraith

182 Steindler, A., Williams, L. A., and Guri, J. P. Tabetic Arthropathies, *Urol & Cutan Rev* 46 633 (Oct) 1942.

183 Amyot, R., Vasquez, J., and Genest, A. Ostéo-arthropathie tabétique de la colonne vertébrale, *Union méd du Canada* 72 305 (March) 1943.

184 Freeman, H. E., and Robertson, J. E. Orthostatic Hypotension Accompanying the Tabetic Form of Dementia Paralytica, *Arch Dermat & Syph* 46 796 (Dec) 1942.

and Meyer <sup>185</sup> support the view that the process underlying the focal manifestations is essentially inflammatory, a localized intensification of the usual pathologic process of dementia paralytica. Vascular changes are admitted to occur, but these, they think, are secondary to the inflammatory process. Histologic studies show that the areas of inflammation, which later become atrophic, are most often situated in the posterior parts of the cerebral cortex.

*Adie's Syndrome*—Adie's syndrome, a symptom complex of absence of tendon reflexes and tonic pupils, is of importance in that it must be differentiated from tabes dorsalis. Dynes <sup>186</sup> describes the clinical aspects of the syndrome. In the series of 8 cases, which he reports, symptoms of nervousness, emotional disturbance, palpitation, sweating and the associated anxiety and fear states frequently were encountered. This confirmed previous observations that instability of the autonomic nervous system is commonly associated with the tonic pupils and areflexia. Blurring of vision, occasional ocular pain or photophobia may accompany the pupillary abnormality. The author stresses the fact that Adie's syndrome is a benign disorder and requires no therapy unless it be psychotherapy, particularly if the patients previously have been told that they suffer from syphilis.

Adie described the pupillotonic phenomena as being unilateral, with the tonic pupil considerably larger than the nontonic pupil. About 80 per cent of the persons affected are females, the majority of them being young. The tonic pupil is usually oval, with either vertical or horizontal orientation. To the usual methods of examining pupils by flashlight the reaction to light, direct and consensual, is completely or almost completely absent. When the person is in the darkness for an hour the pupil dilates, and when he comes into bright light a sluggish contraction may be observed, so that the pupil becomes narrower than before it was in the darkness. The pupil finally contracts to a point where it is smaller than the normal pupil. The Adie pupil is said to dilate readily with mydriatics and to contract with physostigmine.

Adie believes that the factor responsible for the tonic pupil is of sympathetic origin. He agrees that the site of the disturbance of the pupils is the sympathetic part of the nucleus of the third nerve. Adie and many others do not believe that this type of pupil is associated with a syphilitic infection. However, there are those who have not agreed with this impression.

Lowenstein and Friedman <sup>187</sup> have studied true Adie pupils and Adie-like pupils associated with syphilis. They conclude as follows:

1 Pupillotonic reactions may be caused by peripheral lesions of the third nerve both post-ganglionic and preganglionic and by lesions in the great vegetative centers of the diencephalon and their connections with the mesencephalon.

2 Adie's syndrome is due to heredodegenerative disease localized in the great autonomic centers of the diencephalon and their connections with the mesencephalon. It is characterized by pupillotonic reactions with irritative (not paralytic, like the Horner-Bernard syndrome) sympathetic symptoms and absence of tendon reflexes. It generally has no syphilitic etiologic factor but as a syndrome may be produced by so-called asymptomatic syphilis nervosa.

3 As the nervous manifestations of congenital syphilis (more frequently than of acquired syphilis) are frequently localized in the sympathetic center, there is a possibility that in some cases Adie's syndrome is due to congenital syphilis.

4 The pupillographic picture of Adie's syndrome is generally unequivocal.

<sup>185</sup> Galbraith, A. J., and Meyer, A. Lissauer's Dementia Paralytica, J. Neurol. & Psychiat. 5:22 (Jan-April) 1942.

<sup>186</sup> Dynes, J. B. Adie's Syndrome: Its Recognition and Importance, J. A. M. A. 119:1495 (Aug. 29) 1942.

<sup>187</sup> Lowenstein, O., and Friedman, E. D. Adie's Syndrome (Pupillotonic Pseudotabes), Arch. Ophth. 28:1042 (Dec.) 1942.

5 Physostigmine contracts the Adie pupil like the normal pupil, however, it restores the ability of the Adie pupil (in twelve to twenty minutes after its local application) to react to light and to dilate to distant vision

6 The physostigmine test in cases of questionable diagnosis enables one to differentiate Adie's syndrome from similar syndromes due to acquired syphilitic infection

7 Neurotonia characterized by a prompt contraction of the pupil to light but a sluggish and retarded dilation (sometimes after a latency period of more than five minutes) and by a convergence reaction which may be unilaterally or bilaterally diminished or absent appears to be an inversion of Adie's syndrome. The relation with Adie's syndrome is shown by the fact that either syndrome may be substituted for the other in the hereditary sequence, therefore, the basic processes must be considered identical

8 The clinical entities of neurotonia and pupillotonic pseudotabes include many minor and abortive forms which can be detected by pupillography, they are not rare but are rather frequent anomalies and have the value of a focal stigma degenerationis in the nervous system

Leathart<sup>188</sup> discusses the physical signs of Adie's syndrome and the anatomy of the ocular reflexes concerned. The author believes that the physical signs of the syndrome can be produced by destruction of the ciliary ganglion, and he postulates defective conduction between preganglionic and postganglionic fibers in this structure. Also postulated is a lesion in the sacral and lumbar segments of the spinal cord producing the areflexia in the knee and ankle jerks—a lesion in the intercalated fibers connecting the posterior root fibers with the anterior horn cells, possibly resulting in faulty conduction in the synapses there, analogous to the abnormalities in the ciliary ganglion with the loss of the light reflex

*The Catatonic Pupil*—The so-called catatonic pupil is characterized by inequality in size, inconstancy in reaction and sluggishness or complete abolition of the light reflex. Levine and Schilder<sup>189</sup> have studied this pupillary abnormality and believe it is due to paralysis or inhibition of the parasympathetic nervous system. They point out that when a person exerts pressure, as in squeezing some object, both the normal and the catatonic pupil become dilated and less rapidly reactive to light. By this procedure it may be possible to bring out latent pupillary defects. The Argyll Robertson pupil is not affected by the procedure, nor is the tonic pupil of Adie. The effect of mydriatic drugs can be enhanced by the procedure until the drugs cause complete mydriasis

*Pathways of Pupillary Contraction*—Nathan and Turner<sup>190</sup> present evidence to show that there are two efferent pathways for pupillary contraction, one serving the light reflex and the other the accommodation-convergence synkinesia

It is usually believed that pupilloconstrictor fibers leave the nucleus of the third nerve and run with the nerve to the inferior oblique muscle, branching off from this nerve to relay in the ciliary ganglion. Distal to the ganglion they form several short ciliary nerves, which pierce the sclera around the optic nerve and form the ciliary plexus, from which fibers to the sphincter muscles of the iris are derived

If this were the only pathway by which constrictor fibers reach the sphincter, complete interruption of this pathway should cause paralysis of the reaction to light and in accommodation. Cases are described, however, which show that the Argyll-Robertson pupil may be caused by damage to the peripheral efferent path-

188 Leathart, P. W. The Tonic Pupil Syndrome, *Brit J Ophth* **26** 60 (Feb) 1942

189 Levine, A., and Schilder, P. The Catatonic Pupil, *J Nerv & Ment Dis* **96** 1 (July) 1942

190 Nathan, P. W., and Turner, J. W. A. The Efferent Pathway for Pupillary Contraction, *Brain* **65** 343 (Dec) 1942

way to the pupil. Some other pathway must therefore be available. The authors believe this second pathway may run from the third nucleus to the episcleral ciliary ganglion and thence relay to the ciliary body, without passing through the ciliary ganglion.

*Syphilitic Papilledema*—Involvement of the optic nerves in syphilitic meningitis about the optic chiasm has been reported several times in the past. In these cases syphilitic arachnoiditis caused primary atrophy of the optic nerves. Hausman<sup>191</sup> reports the occurrence in 2 patients of syphilitic papilledema without increase in intracranial pressure. When atrophy of the optic nerves appeared it was secondary to the papilledema. In 1 of the cases papilledema was associated with a moderate degree of internal hydrocephalus, dilatation of the chiasmal cistern and thickening of the arachnoid. In the other the cause was a gummatous meningitis around the optic chiasm and nerves. In neither case was there any significant increase in the cerebrospinal fluid pressure.

*Fever Therapy*—The changes produced in cerebral blood sugar, lactic acid and  $p_H$  by elevation of temperature in 12 patients with dementia paralytica being treated by diathermy have been studied by Looney and Borkovic<sup>192</sup>. They report a slight increase in utilization of sugar and a significant increase in  $p_H$ . The arteriovenous difference in lactic acid was reversed so that during the febrile period lactic acid was produced. This may explain, in part, the slight increase in the arteriovenous difference in blood sugar. The findings confirm previous reports that there is no increase in brain metabolism during diathermy.

The use of oxygen during the period of artificial fever therapy has been instituted on the basis that the increase in metabolism coincident with the increase in body temperature requires a greater amount of oxygen than can be acquired by normal respiration. Cullen, Weir and Cook<sup>193</sup> find the use of oxygen during fever therapy beneficial. Patients receiving oxygen have less tachycardia and require less sedatives. Restlessness, mental confusion and excitement are less frequent and less marked than in those who do not receive oxygen.

*Electric Shock Therapy*—After using nonconvulsive electric (faradic) shock therapy for 5 patients with dementia paralytica, Berkwitz<sup>194</sup> reports that acute delirious reactions responded favorably. Subsequent treatment with malaria and chemotherapy resulted in improvement in the clinical signs and in the abnormalities in the spinal fluid.

Electric shock treatment of patients with psychoses associated with dementia paralytica has been attempted by Heilbrunn and Feldman<sup>195</sup>. Five patients whose psychotic manifestations had failed to improve from fever and chemotherapy were chosen. Alternating electric current was employed, the electrodes being applied at the temples. The initial amount of current usually was 250 to 350 milliamperes for three-tenths second at a tension of 60 to 70 volts. The "dosage" was gradually

191 Hausman, L. Syphilitic Papilledema Without Increase in Intracranial Pressure. Its Relation to Lesions at the Chiasm, *J Mt Sinai Hosp* 9 522 (Nov-Dec) 1942.

192 Looney, J. M., and Borkovic, E. J. The Effect of Diathermy on Brain Metabolism. Changes Produced on the Sugar, Lactic Acid and  $p_H$  of the Arterial and Venous Blood of the Brain in Parietic Patients, *J Lab & Clin Med* 28 983 (May) 1943.

193 Cullen, S. C., Weir, E. F., and Cook, E. The Rationale of Oxygen Therapy During Fever Therapy, *Arch Phys Therapy* 23 529 (Sept) 1942.

194 Berkwitz, N. J. Non-Convulsive Electric (Faradic) Shock Therapy of Psychoses Associated with Alcoholism, Drug Intoxication and Syphilis, *Am J Psychiat* 99 364 (Nov) 1942.

195 Heilbrunn, G., and Feldman, P. Electric Shock Treatment in General Paresis, *Am J Psychiat* 99 702 (March) 1943.



increased until a convulsant dose was found. The treatment was given two to three times a week. The procedure proved to be a perilous one. Cardiovascular or respiratory failure necessitated discontinuance of the treatment before any clinical improvement was noticeable. The authors attribute the severe complications to a heightened vulnerability of the ganglion cells of patients with syphilitic meningoencephalitis.

*Malaria Therapy*—Kopp and Solomon<sup>196</sup> call attention to the fact that in therapeutic malaria transient disturbances in hepatic function may be noted. Performing a variety of tests of hepatic function on 9 male patients under treatment for dementia paralytica with inoculation malaria, these authors found indications of decreased hepatic function in reduction in percentages of total blood cholesterol and cholesterol ester, in lowered excretion of hippuric acid and in strongly positive reactions to cephalin flocculation tests. Less marked were reduction of phospholipid, retention of bromsulphthalein and changes in bilirubin. Impairment of hepatic function was transient, usually clearing within three to six weeks after termination of the malaria.

Of interest in the management of syphilitic patients being treated with therapeutic malaria is the observation that jaundice occasionally occurs after termination of the malaria and after the administration of the first few injections of an arsenical. The authors believe that the administration of arsenicals after the malaria treatment and before function of the liver has returned to normal may overburden the liver and result in jaundice.

Sodium bismuth thioglycollate has been shown to reduce the frequency of malarial paroxysms without eliminating them altogether. Young, McLendon and Smarr<sup>197</sup> have sought to determine (1) at what age the parasites are affected by the drug and (2) whether species of malaria parasites other than *Plasmodium vivax* can be controlled similarly. In 0.1 to 0.2 Gm amounts, this compound was found to have an inhibitory effect against *P. vivax* parasites which are half grown, i. e., those obtained about sixteen to twenty-eight hours after a paroxysm. Parasites older or younger were not affected. Use of the drug at this time converted paroxysms from quotidian to tertian periodicity, and paroxysms converted to tertian in type usually remained so during the remainder of the infection. No significant effect of sodium bismuth thioglycollate could be demonstrated against either *Plasmodium malariae* or *Plasmodium falciparum*.

*Intraspinal Injection of Thiamine Hydrochloride*—Stone<sup>198</sup> has administered thiamine hydrochloride intraspinally combined with vitamin E and vitamin B complex orally to 63 patients with neurosyphilis, and he recommends this as a valuable adjunct in the treatment of neurosyphilis. In his experience, patients with tabes dorsalis show marked improvement in gait, symptoms involving the bladder, visual disturbances and lightning pains. In patients with dementia paralytica an increased tolerance to fever therapy was noted and fewer hours of fever were needed to produce a remission. There was, however, no definite effect on the psychoses of patients who failed to improve under previously administered fever therapy following additional intraspinal and oral vitamin medication.

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196 Kopp, I, and Solomon, H. C. Liver Function in Therapeutic Malaria, *Am J M Sc* **205**:90 (Jan) 1943

\* 197 Young, M. D., McLendon, S. B., and Smarr, R. G. The Selective Action of Thio-bismol on Induced Malaria, *J A M A* **112** 492 (June 19) 1943

198 Stone, S. Non-Specific Therapy of Neurosyphilis. Results from Intraspinal Administration of Thiamin Chloride Combined with Vitamin B Complex and Vitamin E (Wheat Germ Oil), *Urol & Cutan Rev* **46** 714 (Nov) 1942



*Cisternal Puncture*—Over a period of ten years, 6,123 diagnostic cisternal punctures have been performed at the Dallas Syphilis and Venereal Disease Clinic. Alexander, Fox and Schoch<sup>199</sup> report that in this series no fatalities have resulted nor any reaction of serious consequence. Few of the patients, all of whom were ambulatory, had headaches which were severe enough to cause them to complain, and no headaches were so severe as to require rest in bed. The authors believe that in competent hands cisternal puncture is a valuable procedure, which should be more widely used. They do not consider the procedure too dangerous for routine use.

*Post-Lumbar-Puncture Headache*—Favorable results from the treatment of post-lumbar-puncture headache with ergotamine tartrate are reported by Guttman<sup>200</sup>. Thirty-five patients on whom lumbar puncture had been performed and spinal anesthesia induced were treated for post-puncture headache with this drug (0.25 to 0.50 mg, given either intravenously or intramuscularly). When given according to the tolerance of the patient, ergotamine tartrate was found to be of value in relieving headache in 80 to 90 per cent of the persons treated.

#### CONGENITAL SYPHILIS

*Dental Changes*—A comprehensive review of the dental changes in congenital syphilis is presented by Sarnat and Shaw<sup>201</sup>. A group of 73 patients with congenital syphilis was studied, and 22 (30 per cent) were found to have characteristic dental changes.

The effects of the disease are different in the growing deciduous and permanent teeth. The deciduous teeth, active in the formation of enamel, show developmental disturbances in that structure, the permanent teeth, active in morphodifferentiation, show disturbances at the dentoenamel junction, with a resulting characteristic dwarfing of the crown. The pathognomonic convergence of the lateral surfaces of the permanent upper central incisors should not be confused with hypoplasia of the enamel, which occurs at a later time and which may be caused by rickets, hypoparathyroidism or fluorosis.

The teeth which are affected and may be of diagnostic value in congenital syphilis are the permanent upper central incisors, lower central and lateral incisors and first molars. Both the incisors and the first molars were found to have a convergence of the lateral surfaces. In addition to decreased occlusal surface of the permanent first molars, the cusps frequently are crowded together, and caries not uncommonly is superimposed. Dental dystrophy occurs early and is permanent.

A comparison of the ground sections of Hutchinson teeth and of normal incisors revealed differences in the size and form of the dentoenamel junctions but no significant structural differences in the enamel and dentin. Roentgenographic examination revealed the characteristic convergence of the sides of incisors and molars, and this abnormality was demonstrable prior to eruption of the teeth.

*Saddle Nose Deformity*—A not infrequent facial deformity resulting from syphilitic infection, either congenital or acquired, is the saddle nose. Persons afflicted with this unsightly deformity benefit both physically and mentally from operative correction. Fleming<sup>202</sup> discusses the operative technic for the correction.

199 Alexander, L. J., Fox, E. C., and Schoch, A. G. Cisternal Puncture. Favorable Report Based on Over Six Thousand Punctures, *Arch Dermat & Syph* **46**: 725 (Nov) 1942.

200 Guttman, S. A. Treatment of Post-Lumbar-Puncture Headache with Ergotamine Tartrate, *Arch Neurol & Psychiat* **49**: 556 (April) 1943.

201 Sarnat, B. G., and Shaw, N. G. Dental Development in Congenital Syphilis, *Am J Dis Child* **64**: 771 (Nov) 1942.

202 Fleming, P. N. The Saddle Nose, *Dis Eye, Ear, Nose & Throat* **2**: 244 (Aug) 1942.

of the saddle nose deformity, stressing adequate preoperative preparation, meticulous aseptic technic and the fact that several procedures may be necessary before a satisfactory result is attained. To fill in the bony defect the author recommends implantation of a small piece of ivory, rib cartilage or tibial graft. Of these, ivory offers the best cosmetic result, since it can be readily shaped and may be sterilized before use.

*Effect of Bismuth on Growth of Bone*—Administration of bismuth in amounts such as are used in the treatment of patients with syphilis causes abnormalities at the site of provisional ossification of growing long bones. These abnormalities appear to consist chiefly of the persistence of matrix substance at the metaphysial line beyond the time when normally it would be removed. These metaphysial changes occur only when bone is still in the process of growth.

Because these bony abnormalities occur at the area of growth of the long bones and because linear growth of the body is dependent on osseous growth, Russin, Stadler and Jeans<sup>203</sup> have studied the effect of long-continued antisyphilitic therapy on the stature of children. They interpret their data as showing that antisyphilitic treatment has no adverse effect on ultimate bone or body length. Of the 10 children included in the study, the majority grew at average rates. Five exceeded the predicted height by 2 inches (5 cm) or more, and three had heights 2 or more inches less than predicted. For the entire group the average difference between actual and predicted height was zero.

*Cardiovascular Involvement*—In a lengthy and detailed review of the literature pertaining to cardiovascular involvement in congenital syphilis, Hinrichsen<sup>204</sup> concludes

Reports in the literature show that congenital syphilis produces definite myocardial lesions of two types, namely, interstitial and nodular myocarditis, in which spirochetes can be demonstrated. No evidence can be found that congenital syphilis produces valvular heart lesions. The role of this disease in the production of aortitis and aneurysm and in the production of congenital malformations of the heart has not been determined definitely. Further study is required. Syphilitic arteritis, particularly cerebral arteritis, may be produced by congenital syphilis. It is possible that congenital syphilis is a factor in the production of arteriosclerosis and of Raynaud's disease. Congenital syphilis is one of the causes of hemorrhagic disease in the newborn infant.

*Resemblance to Erythroblastosis*—Having studied 53 infants with erythroblastosis, Henderson<sup>205</sup> discusses the differentiation between this condition and congenital syphilis. The two diseases have several features in common: frequent occurrence of premature birth, erythropoietic response to toxic hemolysis, cirrhosis of the liver and placental abnormalities. It is pointed out that serologic tests for syphilis, the demonstration of *S. pallida* or the occurrence of osteochondritis may assist in the differentiation. The tendency is for congenital syphilis to become progressively less severe in succeeding pregnancies, whereas in erythroblastosis the trend is in the opposite direction.

*Treatment with Acetarson*—In the past decade, much has been written about the treatment of congenital syphilis with acetarson. Preliminary reports were favorable, even enthusiastic, but more recently the effectiveness of this oral

203 Russin, L. A., Stadler, H. E., and Jeans, P. C. The Bismuth Lines of Long Bones in Relation to Linear Growth, *J. Pediat.* **21** 211 (Aug.) 1942.

204 Hinrichsen, J. Cardiovascular Involvement in Congenital Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **27** 319 (May) 1943.

205 Henderson, J. L. Erythroblastosis or Congenital Syphilis? Observations on Erythroblastosis and Its Differential Diagnosis from Congenital Syphilis, *J. Obst. & Gynaec. Brit. Emp.* **49** 499 (Oct.) 1942.

spirocheticide has been questioned. Arena<sup>206</sup> reviews the advantages of acetarsone as well as the objections that have been raised to its use. In his own experience, the oral use of acetarsone is both advantageous and effectual. This route of administration should be used for infants under 1 year of age, since mothers will carry out the treatment. Older infants should be given arsenicals parenterally, since the injections can be given without undue difficulty and the results are better.

In monographic form, published as a supplement to *Veneral Disease Information*, Hinrichsen<sup>207</sup> reviews the literature pertaining to the use of acetarsone in the treatment of congenital syphilis. The experimental studies of the drug in animals, its toxic effects in adults, and its therapeutic effect in adult syphilis are considered in detail because of the direct relationship they bear to the problem of treatment of congenital syphilis. Most observers are agreed that the antisyphilitic action of acetarsone is considerably inferior to that of arsphenamine. Some have found its action to be about the same as that of bismuth, while others consider its action inferior to that of bismuth. The only apparent reason for the use of acetarsone in the treatment of congenital syphilis is the fact that it can be given by mouth. This advantage is offset, however, by the fact that the physician can never be sure that the treatment prescribed actually has been given.

The results of experimental studies of acetarsone in animals show marked variations in toxicity as determined by different investigators and also among the animals of any single investigator. The same variable and unpredictable results were obtained in the prophylactic and curative treatment of animals infected experimentally. That acetarsone is a highly toxic drug is apparent from the number and severity of the toxic reactions which have been reported to occur both in adults and in children. Analysis of the therapeutic results with the drug is difficult because of the many extraneous factors.

The author believes that all the evidence on hand supports the contention that acetarsone is far from being the "ideal" drug for the treatment of infantile congenital syphilis and that it is of very limited usefulness in syphilotherapy.

*Treatment with Mapharsen*.—Astrachan and Cornell<sup>208</sup> find mapharsen an effective drug for the treatment of both early and late congenital syphilis. In their opinion, the dosage of mapharsen should not exceed 0.75 mg per kilogram of weight.

Of 68 patients with congenital syphilis, 57 were in the late stages of the disease and 11 in the early stages. These patients received a total of 1,507 injections of mapharsen, 495 of these being administered intramuscularly. Few untoward reactions were noted, and the authors believe the drug is even less toxic to children than to adults.

As to the feasibility of intramuscular administration of mapharsen, it is stressed that, while some patients complained of severe and persistent pain at the site of injection, the majority of the injections were followed by slight or moderate pain only, that no areas of necrosis developed and that serious systemic complications did not appear as a result of this method of administration. In selected cases, the intramuscular route may be used, but it should be employed cautiously, with

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206 Arena, J. M. The Treatment of Congenital Syphilis with Acetarsone (Stovarsol). The Result of a Ten-Year Study, *South M J* 36:201 (March) 1943.

207 Hinrichsen, J. Acetarsone in the Treatment of Congenital Syphilis, *Ven Dis Inform*, 1942, supp 18, p 1.

208 Astrachan, G. D., and Cornell, V. Mapharsen in the Treatment of Congenital Syphilis, with Especial Consideration of the Intramuscular Method of Administration, *J A M A* 121:746 (March 6) 1943.

gradually increasing doses, and only in those cases in which all attempts at intravenous therapy have failed

*Congenital Syphilis as a Cause of Infant Mortality*—A comparative mortality study in 859 cases of premature birth at the Charity Hospital of Louisiana for a period of the years 1937 to 1940 inclusive is given by Flax, Levert and Strong<sup>209</sup> The mortality rate among premature infants in 1937 was 85.3 per cent, and in 1940, 42.2 per cent There was a gradual yearly decrease in the mortality rate, which could be accounted for primarily on the better care of premature infants

There were 498 deaths of premature infants in the entire group The main causes of death were as follows: atelectasis, 24.22 per cent, prematurity, 22.08 per cent, bronchopneumonia, 15.07 per cent, diarrhea, 12.44 per cent, cranial injury, 11.05 per cent, syphilis, 4.61 per cent, and all other causes, 10.44 per cent In some instances it was impossible to arrive at any diagnosis other than prematurity

*Third Generation Syphilis*—The question of the transmission of syphilis to the children of those who themselves have acquired the disease in utero (third generation syphilis) is still debatable Beerman, Wammock and Magnuson<sup>210</sup> have analyzed the cases of third generation syphilis published since 1933, noting that in no instance has a really indubitable example been recorded They discuss in detail a patient whose clinical course and whose parents' and grandparents' infections were studied carefully The patient, in all probability, had third generation syphilis

#### SYPHILIS AND OTHER DISEASES

*Syphilis and Cancer*—A study has been made by Levin and his co-workers<sup>211</sup> to determine the relationship between syphilis and cancer by determining the prevalence of reported syphilis among patients with cancer reported to the New York State Health Department The data appear to confirm the previously reported high prevalence of syphilis among males with cancer of the tongue and among white females with cancer of the cervix

Evidence for the diagnosis of syphilis consisted of (a) physical manifestations of tertiary syphilis in 26 cases, (b) at least two positive serologic reactions and a history of infection or treatment in 39 cases, (c) a single positive serologic reaction and a history of infection or treatment in 12 cases, (d) at least two positive serologic reactions in 42 cases, and (e) a single positive serologic reaction alone in 58 cases

Among males with cancer of the tongue, the prevalence of syphilis was approximately five times as great as among males with cancer of all other sites Among females with cancer of the cervix, the corresponding ratio was 3.5 to 1 The factors of age, sex, color and marital status failed to account for the excess prevalence of syphilis in these two groups

Recent information concerning biologic false positive serologic reactions suggests, however, that the supposed association of syphilis with cancer of the tongue or cervix may be more apparent than real, perhaps due to the fusospirochetosis often associated with cancer in these areas

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209 Flax, L., Levert, E. L., and Strong, R. A. A Study of Premature Mortality, *J Pediat* **21**:717 (Dec) 1942

210 Beerman, H., Wammock, V. S., and Magnusen, K. B. Third Generation Syphilis: Review of the Recent Literature and Report of a Probable Case, *Am J Syph, Gonorr & Ven Dis* **26**:504 (July) 1942

211 Levin, M. L., Kress, L. C., and Goldstein, H. Syphilis and Cancer: Reported Syphilis Prevalence Among 7,761 Cancer Patients, *New York State J Med* **42**:1737 (Sept 15) 1942

*Syphilis and Lymphogranuloma Venereum*—Mixed infections with syphilis and lymphogranuloma venereum have been studied in detail by May, whose most recent publication<sup>212</sup> throws new light on the association of these two diseases. May believes that when syphilis is accompanied by lymphogranuloma venereum certain characteristic changes in the early lesions of the former disease become manifest. These changes include clinically detectable lymphangitis, earlier and more extensive local edema and regional lymphadenopathy, changes in the color and shape of the primary chancre, increased local pain and, in general, a more extensive local disease. There is some evidence that the secondary lesions of syphilis may be more diffuse and malignant, and possibly more resistant to treatment. As yet there is no reason to believe that the mixed infection results in more frequent or more precocious involvement of the central nervous system or of the cardiovascular apparatus.

Grace, Shaffer and Rake<sup>213</sup> have found that serums from patients with congenital syphilis who have negative Frei reactions do not fix complement in the presence of antigen from lymphogranuloma venereum virus. Since this contrasts with the frequent occurrence of positive reactions obtained with serums from patients with venereally acquired syphilis, the authors are further confirmed in their belief that during exposure to venereal infection resulting in syphilis a concomitant and often latent infection with lymphogranuloma venereum frequently occurs.

*Penile Amebiasis*—Of interest in the differential diagnosis of genital lesions in general and of primary syphilis in particular is the report by Hermann and Berman<sup>214</sup> of a penile ulcer supposedly due to *Endamoeba histolytica*. Their patient was known to have had amebic dysentery, and amebas were found in the stool. The exudate from the penile ulceration also contained encysted forms of *E. histolytica*, and the lesion healed after the local use of carbarsone. Serologic reactions for syphilis became positive as the lesion developed, but no therapeutic response to antisypilitic treatment had been noted, and repeated dark field examinations of the ulcer gave negative results. It seems somewhat incongruous that the encysted form of the parasite are reported, as one might expect trophozoites if the active ulceration were due to amebiasis. The possibility of a biologic false positive reaction for syphilis apparently was not considered.

212 May, J. Nueva contribucion al conocimiento de la asociacion sifilo-protademoico, *Rev argent de dermatosis* **26** 513, 1942.

213 Grace, A. W., Shaffer, M. F., and Rake, G. Further Evidence Concerning the Specificity of the Lymphogranuloma Venereum Complement-Fixation Test in Syphilis, *Am J Syph, Gonorr & Ven Dis* **27** 44 (Jan) 1943.

214 Hermann, H. B., and Berman, L. S. Penile Ulcer Caused by *Endamoeba histolytica*, *J A M A* **120** 827 (Nov 14) 1942.

## Book Reviews

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**Diagnosis of Uterine Cancer by the Vaginal Smear** By George N Papanicolaou, M D, and Herbert F Traut, M D Price \$5 00 Pp 47, with 11 color plates New York Commonwealth Fund, 1943

The purpose of this book is directed toward the establishment of an early diagnosis of uterine cancer Every one appreciates the fact that further improvement in the methods of treatment of uterine cancer is dependent on the establishment of an earlier diagnosis

The procedure recommended is of value, as demonstrated by the descriptions and records It is to be used, as the authors state, as an accessory procedure in conjunction with biopsy, curettage and other methods If it is employed in this manner, it is apparent that a diagnosis can be made earlier than has been customary

The principal difficulty with the vaginal smear procedure is that there are relatively few workers who have had sufficient experience to interpret accurately the findings The authors were reticent in making final interpretation of their observations until they had acquired a vast experience In a real effort to transmit their experience to others, they have used the only practical method, namely, presentation of many excellent colored drawings and photomicrographs

The detailed descriptions, the straightforward presentation of the findings and interpretations and the great number of good drawings and photomicrographs make this book of great value to both research workers and clinicians who are interested in vaginal smear studies and the early diagnosis of uterine cancer

**Reaction to Injury** By Wiley D Forbus Price, \$9 00 Pp 797, with 532 figures Baltimore Williams & Wilkins Company, 1943

It is no mean task to produce an entirely new textbook of pathology, and the author is to be congratulated on his achievement The present handsome volume, well printed and profusely illustrated with excellent reproductions of gross and microscopic lesions, constitutes according to the publisher's notice only one half of Dr Forbus' task Another section is to appear later, this first instalment deals "with the nature and causation of disease and with the resistive reaction the inflammatory process and all the diseases that arise therefrom" Matters such as tumors will doubtless be dealt with in the subsequent volume The author approaches his subject from a dynamic standpoint (witness the title), but in the end one looks for good discussions of morphology and histology, and these are very well done Space might well have been saved by shortening or omitting most of the clinical discussions, which are a duplication of what is found in any textbook of medicine

**Addendum to the Chemistry of the Amino Acids and Proteins** Edited by Carl L A Schmidt Price, \$5 00 Pp 255 Springfield, Ill Charles C Thomas, Publisher, 1943

Instead of a revision of the "Chemistry of the Amino Acids and Proteins," this addendum was published It brings up to date some of the salient advances made in the field of protein chemistry since 1937, when the original book was written

Practically every chapter has been revised and corrections made on the original text At the end of each chapter there is a complete bibliography of the publications from which the data were drawn The authors have adhered to their previous level of clear presentation of their respective problems The addendum is certainly to be recommended to all who are interested in the advances in protein chemistry for the past four years It is really a small book in itself, written by investigators active in the field The authors should be encouraged to keep the book up to date, perhaps preferably by making a complete revision of the original book in the future, if possible

**Clinical Parasitology** By Charles Franklin Craig and Ernest Carrol Faust Third Edition Price, \$9 Pp 750, with 284 engravings and 4 colored plates Philadelphia Lea and Febiger, 1943

This handsomely gotten up book of 750 pages is too long to review in detail However, the names of Craig and Faust would seem to promise a happy combination of expert knowledge on the subject of clinical parasitology The book is comprehensive, well written and excellently illustrated There is a thorough bibliography The section on arthropods and human disease seems specially valuable, as this part of the subject is slighted in many textbooks

**An Introduction to Medical Mycology** By George M Lewis and Mary E Hopper  
Second Edition Price, \$6.50 Pp 342 Chicago The Year Book Publishers, Inc

It is pertinent that a simplified, yet complete, manual on human mycology be available at this time, as there is a marked increase in the incidence of mycotic disease among the members of the armed forces. Dermatophytosis and other mycotic diseases among these men often produce considerable disability and loss of valuable time.

The first edition of this book was printed four years ago and has become well accepted as a guide to elementary human mycology. The second edition has been enlarged and rewritten in part. There are many added colored and halftone illustrations. The chapters on the passive transfer test and the data on the trichophytin, oidiomycin, coccidioidin, blastomycin and sporothricin tests, as well as the information on histoplasmosis, have been brought up to date. The authors have simplified the classification of fungous diseases so that the way is cleared for ready diagnosis by those who have only a practical interest in human mycology. They have gathered and simplified the available practical methods of diagnosis and therapeutics on human mycology and have evaluated these procedures in the light of their own extensive experience.

The book is divided into two parts. The first deals with the clinical, theoretic and experimental aspects of mycology, and the second deals with laboratory methods useful for the diagnosis of fungous diseases. The latter section presents detailed and precise methods for identifying fungi. The exact formulas for the simpler types of culture mediums are given. Directions for the construction, purchase and diagnostic use of filtered ultraviolet rays are presented. All procedures advised are simple and practical for office use. At the end of each chapter there is a short bibliography which is sufficiently inclusive to give ready access to the available literature on those subjects discussed. None of the discussions are long or involved or inclusive enough to permit a detailed or complete consideration of any one subject. For complete information the reader must resort to the bibliography. The book is to be recommended as a good elementary manual of practical human mycology.

**Rehabilitation of the War Injured** Edited by William Brown Doherty and Dagobert D Runes Price, \$10 Pp 684, with 240 figures New York The Philosophical Library, 1943

This symposium includes over fifty articles on various aspects of rehabilitation. The main subject headings concern neurology and psychiatry, reconstructive and plastic surgery, orthopedics, physical therapy, occupational therapy and vocational guidance, and legal aspects of rehabilitation. Such names as Denny-Brown, Stanley Cobb, Vilray Blair, Frank Krusen and William Lennox among the authors give an idea of the authoritative character of the work, although most of the articles are fairly brief and general. The volume is well printed but rather poorly illustrated. An index would be useful.

**The Common Form of Niacin Amide Deficiency Disease Aniacinamidosis** By William Kaufman Price, not given Pp 62 Bridgeport, Conn Yale University Press, 1943

This little volume, privately printed, expresses the views of the author on nicotinic acid deficiency, a condition which he refers to as "aniacinamidosis." An elaborate syndrome is described. The author himself states that "lacking adequate laboratory facilities I can submit no rigorous clinical or laboratory proof" that the conditions described are entirely due to niacin deficiency.



## RECURRENT LYMPHOCYTIC CHORIOMENINGITIS

REPORT OF A CASE IN WHICH TREATMENT WAS WITH  
POOLED NORMAL ADULT SERUM

JEROME V TREUSCH, M D

ALBERT MILZER, P H D

AND

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CHICAGO

The following case is reported because it included many unusual clinical manifestations and is the first case of lymphocytic choriomeningitis to our knowledge in which an attempt was made to treat the disease with pooled normal adult serum

### REPORT OF CASE

B D, a 22 year old student nurse, was admitted to Michael Reese Hospital on May 4, 1941. Her past history contained nothing of medical significance except for a "sleeping episode" five years previously, while she was living in El Cajon, San Diego County, Calif. The only additional information obtainable was that the patient had an "unpleasant disposition" at that time, from which she recovered.

The patient had been perfectly well until 10 p m on May 4, 1941, when, after taking a long walk and returning to her room, she felt faint, with palpitation and tachycardia. She became apprehensive and then fainted.

Immediate examination revealed the patient to be in apparent deep coma, completely flaccid and unresponsive to stimuli. Her respirations were rapid and shallow. The pulse was rapid, with a rate of 110 to 130 per minute, and the blood pressure was 130 systolic and 80 diastolic. General physical examination gave essentially negative results. The deep reflexes were all present, equal and hyperactive, and there were no pathologic reflexes. During the succeeding several hours the patient was roused from her stupor for periods of a few moments, but she appeared dazed and only at times seemed lucid. She could be awakened by a very loud noise or a painful stimulus, after which her attention could be sustained by conversation.

The following morning the patient could be aroused and had less difficulty remaining awake. She appeared rational in her responses but was not alert. On the evening of May 6, the patient again became deeply stuporous and could not be aroused during the night. The following morning she could again be aroused, although she remained apathetic and indifferent. On the morning of May 7, while she was being examined, weakness suddenly developed in the right lower two thirds of the face, the right arm and the right leg. There was no spontaneous movement on the right side. The reflexes of the right arm were diminished, the abdominal reflexes were absent on the right side, and there were positive Babinski, Gordon and Oppenheim signs on the right. The Beever sign was positive to the left. The Hoover sign was typical of organic weakness of the right leg. There was complete hemianesthesia to touch, pain, temperature, pressure and position of the right side of the face and the body, anteriorly and posteriorly, with a midline demarcation. In attempting to walk the patient fell to the right. There was definite ataxia on the right side. Examination of the cranial nerves disclosed a loss of conjugate deviation of the eyes to the right, right homonymous hemianopsia, normal pupillary responses to light but sluggish responses in accommodation, paresis of the right side of the face of the central type, complete middle ear deafness on the

From the Samuel Deutsch Serum Center, Michael Reese Hospital.

This case is reported with the permission of Dr H F Binswanger and Dr J Reich, attending physician and neurologic consultant, respectively, of the hospital nurses' service of Michael Reese Hospital.



right side (present since a mastoidectomy on that side six years before), protrusion of the tongue to the left, deviation of the jaw to the left and anesthesia of the right side of the face. A lumbar puncture performed at this time yielded fluid essentially normal (table 1). Other laboratory findings are summarized in table 2. Roentgenograms of the chest and the head were essentially normal.

The following day, slight rigidity of the neck and the back developed, with pain in the neck and down the back on attempted flexion of the neck. The Kernig sign was positive bilaterally.

In the subsequent forty-eight hours, the weakness and neurologic symptoms progressed. Extreme apathy continued. On the morning of May 11, the patient became stuporous and

TABLE 1—Findings in the Cerebrospinal Fluid

Date	5/7/41	5/11/41	6/9/41
Ross Jones test	Negative	Negative	Negative
Total cells per cubic millimeter	1	2	1
Lymphocytes, per cent	100	100	100
Lange colloidal gold curve	1111100000	0000000000	1111000000
Sugar, mg per 100 cc	69		69
Chlorides, mg per 100 cc	772		763
Protein, mg per 100 cc	30		32
Culture and smear	Negative	Negative	Negative
Wassermann and Kahn tests	Negative	Negative	Negative
Pressure, cm of fluid	12	6	12
Response to compression of jugular vein	Normal	Normal	Normal

TABLE 2—Summary of Laboratory Data

Date	5/7/41	5/9/41	5/11/41	5/12/41	5/14/41	6/9/41	6/13/41
Blood chemistry	Normal	Normal	—	—	—	—	Normal
Red cell count	Normal	—	Normal	Normal	Normal	Normal	—
White cell count, per cubic millimeter	10,330	—	8,000	23,200	10,700	5,900	—
Differential white cell count, per cent							
Neutrophils	68	—	70	92	73	69	—
Lymphocytes	27	—	25	4	22	28	—
Eosinophils	0	—	0	0	2	6	—
Monocytes	5	—	5	4	3	5	—
Basophils	0	—	0	0	0	2	—
Blood cultures	No growth	—	No growth	—	—	—	No growth
Sedimentation rate	—	—	—	—	—	—	23 mm per hour
Agglutination tests							
Typhoid	—	—	—	—	—	—	Negative
Paratyphoid A and B	—	—	—	—	—	—	Negative
Brucella abortus	—	—	—	—	—	—	Negative
Brucella melitensis	—	—	—	—	—	—	Negative
Heterophil	—	—	—	—	—	—	1/32
Wassermann and Kahn reactions of blood	Negative	—	—	—	—	—	Negative
Urinalysis	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Examination of stool	Normal	—	—	—	—	—	Normal

unresponsive. The respirations were slow and shallow. In addition to the complete hemianesthesia and hemiplegia, the left extremities were flaccid. No deep reflexes could be elicited in the left arm, but they were present in the left leg. The patient was awakened by firm supraorbital pressure and gave monosyllable responses to questions. There was a definite weakness of the left arm and left leg, pronounced stiffness of the neck and a strongly positive Kernig sign bilaterally, a complete external ophthalmoplegia, absence of pupillary reaction in accommodation, though the response to light was normal, and a gross defect in the left field of vision as well as in the right.

During the day the patient became more stuporous and totally blind, and the respirations dropped to 9 per minute. The patient's condition appeared critical, and she was given 2,000 cc of a 10 per cent solution of dextrose in distilled water during the afternoon. At 9 p. m. on May 11, she was given 500 cc of pooled normal adult human serum intravenously in the course of three hours. One-half hour after the serum had been injected, the patient had a chill, during which time her right side moved with the chill. At the same time she became lucid, in marked contrast to her condition previously. Her temperature rose to 102.2 F after the chill and dropped promptly the following morning.

The following morning, the patient was clear mentally. Sensation was normal throughout, there was improved strength in the right arm and leg, and the abdominal reflexes had returned on the right side. There was a normal plantar response on the right. The external ophthalmoplegia had almost disappeared, and accommodation responses were almost normal. The paralysis of the right side of the face was definitely less, and there was midline protrusion of the tongue. Meningeal signs were less pronounced. An additional 500 cc of serum was administered. No pyrogenic reaction followed this administration. Rapid improvement continued, and the following morning, thirty-two hours after the first injection of serum, recovery appeared almost complete.

The patient continued to convalesce for the next ten days. There was only a low grade fever, the temperature rising to 99.6 F, from May 17 to 21. Her recovery was not complete, however, because there were a residual slight weakness of the right extremities, noticeable dragging of the right leg and a positive Romberg sign. The patient did not have normal "associated movement" of the right arm on walking, and she became fatigued easily.

For the next ten days the condition remained unchanged. The patient had severe headaches during the latter part of the period and was reluctant to be up and about.

On the morning of June 8, she again was found in a deep sleep. Although she could be easily aroused and was coherent and oriented, she had difficulty in remaining awake. All findings at this time were normal. At 1:15 p.m. her respiratory rate dropped to 4 per minute, with slight cyanosis. The stupor was deep, and she rapidly acquired paresis of the right side of the face, deviation of the tongue to the right on protrusion and diminished abdominal reflexes on the right. She was in a deep stupor and could be aroused at times only by firm supraorbital pressure. She was given 2,000 cc of a 5 per cent solution of dextrose in saline solution that afternoon. At midnight her coma was deep. Respirations were at a rate of 5 per minute, with occasional deep sighs. The extremities were limp, without response to pinprick. The ocular fundi were normal.

The following morning, the patient awoke spontaneously. At this time the neurologic findings were not as marked as previously. The patient wavered between stupor and semi-stupor the rest of the day. That evening, with the respiratory rate down to 4 per minute, 500 cc of pooled normal adult serum was administered. After the administration, the patient again awoke spontaneously, stating that she felt better, although she had a severe headache. This time she appeared alert and lucid, with spontaneous responses and normal reactions. The neurologic examination at this time revealed no abnormality. One hour later the patient had a chill, followed by a slight rise of temperature in about two hours, the temperature returned to normal the following morning. It is significant that there was subjective and objective recovery preceding the elevation of temperature.

The patient's convalescence in the next two and a half weeks was completely uneventful except for a herpes simplex on the upper lip which developed on June 12. At the time of her discharge she was bright and happy, her emotional and personality responses were normal, and recovery appeared to be complete. The patient was in good health when last seen, one and a half years after her illness.

#### VIRUS STUDIES

Evidence that our stock guinea pigs and albino Swiss mice were free from latent choriomeningitis infection has been presented by one of us (A. M.) in the earlier publications.<sup>1</sup> As previously, rectal thermometers used in taking temperatures of guinea pigs were routinely disinfected in solution of formaldehyde U. S. P. diluted 1 to 10, to prevent possible intrarectal transmission.

Cerebrospinal fluid collected from the patient on May 8, 1941 (four days after the onset of symptoms) was inoculated subcutaneously (1.5 cc) into 2 normal guinea pigs and intracerebrally (0.03 cc) into 6 albino Swiss mice. One cubic centimeter of the fluid which was seeded into various aerobic and anaerobic culture mediums and incubated at 37 C showed no bacteriologic growth in fourteen days. The first guinea pig had fever (temperature 104.7 F) on the eighth day after inoculation and was killed on the thirteenth day, when moribund. The second guinea pig's temperature rose to 104.2 F on the tenth day, and it was found dead on the sixteenth day. At necropsy the brains of both animals were grossly congested, and areas of interstitial bronchopneumonia were seen in stained sections of the lungs. No bacteria were isolated from the brain tissues or heart blood of either guinea pig.

1 (a) Milzer, A. Studies on the Transmission of Lymphocytic Choriomeningitis Virus by Arthropods, *J. Infect. Dis.* **70** 152-172 (March-April) 1942. (b) Milzer, A., and Levinson, S. O. Laboratory Infection with the Virus of Lymphocytic Choriomeningitis. A Two Year Study of Antibody Response, *J. A. M. A.* **120** 27-30 (Sept. 5) 1942.

All of the 6 inoculated mice had rough coats, tremors and tonic convulsions typical of lymphocytic choriomeningitis<sup>2</sup> in seven to nine days after inoculation. Two mice died on the eighth day, while the rest recovered and were subsequently immune to challenge intracerebral inoculation of 1,000 minimal lethal doses of the J P strain<sup>3</sup> of choriomeningitis virus.

Virus recovered from each guinea pig was subsequently identified as that of lymphocytic choriomeningitis by means of a neutralization test with human choriomeningitis convalescent serum. The technic of the neutralization test used has been described in an earlier paper.<sup>1a</sup> Positive controls consisting of known virus plus immune serum and negative controls consisting of virus plus normal serum were included in all neutralization tests.

The second specimen of cerebrospinal fluid collected from the patient during the recrudescence on June 8 (thirty-four days after the initial attack) was inoculated subcutaneously (1 cc) into 2 guinea pigs and intracerebrally (0.03 cc) into 4 albino Swiss mice. No bacteria were isolated from the spinal fluid. One guinea pig had pyrexia (temperature, 104.6 F) on the tenth day following inoculation and was killed five days later, when moribund. The second guinea pig had a temperature of 105 F on the eleventh day and was killed, when moribund, on the sixteenth day. Pathologic changes in the brain and lungs of both animals were typical of lymphocytic choriomeningitis.<sup>4</sup> The animals' brain tissues and heart blood were bacterially sterile, and virus recovered from each guinea pig was positively identified by neutralization tests. The inoculated mice had rough coats and tremors seven to ten days after inoculation but recovered and subsequently resisted intracerebral inoculation of 1,000 minimal lethal doses of the J P strain of choriomeningitis virus.

After being maintained by subcutaneous inoculation in guinea pigs for ten passages, the new strains were titrated for infectivity. It was found that the first strain isolated (D-1) would consistently kill guinea pigs when 0.5 cc of a  $10^{-4}$  dilution in buffered solution of sodium chloride was inoculated subcutaneously. On the other hand, the second strain isolated (D-2) seemed to be more pathogenic, because it killed in  $10^{-6}$  dilutions.

Further studies showed that there was complete cross immunity between the newly isolated strains from the patient and the J P, A M<sup>1b</sup> and W E (Rivers) strains, proved by resistance to 1,000 minimal lethal doses of virus given intracerebrally in albino Swiss mice which had been infected and had recovered. Histologic examination of stained sections of the brains of guinea pigs and white mice that succumbed to the new strains revealed round cell infiltration of the meninges and choroid plexus identical with that produced by the W E (Rivers)<sup>2</sup> and J P strains of virus.<sup>3</sup> Filtration experiments have shown that the new strains suspended in nutrient broth of pH 7.2 (5 per cent brain tissue suspension) readily pass through Berkefeld N and W candles at a negative pressure of 35 cm of mercury.

#### IMMUNOLOGIC STUDIES ON THE PATIENT'S BLOOD SERUM

Serum collected from the patient on August 5 (eighty-seven days after the onset of symptoms) failed to neutralize the newly isolated and J P strains of virus. The complement-fixing antibody titer was 1/40 (serum dilution), with a saline extract of pooled infected guinea pig spleens used as the antigen.<sup>5</sup> Known positive and negative controls were included in complement fixation as well as neutralization tests.

Five months (October 8) after the onset of the disease the patient's serum showed slight protection against the isolated and J P strains. The complement-fixing antibody titer was 1/80. In other tests the serum failed to neutralize the B A I strain of the western type of equine encephalomyelitis virus,<sup>6</sup> but showed strong neutralization of the D 219 strain of St. Louis encephalitis virus.<sup>7</sup> Howitt's technic<sup>8</sup> was followed in the protection tests with the equine encephalomyelitis and St. Louis encephalitis viruses.

2 Rivers, T. M., and Scott, T. F. McN. Meningitis in Man Caused by a Filterable Virus. II. Identification of the Etiologic Agent, *J. Exper. Med.* **63** 415-432 (March) 1936.

3 Leichenger, H., Milzer, A., and Lack, H. Recurrent Lymphocytic Choriomeningitis Treated with Sulfanilamide. Isolation of Virus, *J. A. M. A.* **115** 436-440 (Aug. 10) 1940.

4 Findlay, G. M., and Stern, R. O. Pathological Changes Due to Infection with the Virus of Lymphocytic Choriomeningitis, *J. Path. & Bact.* **43** 327-338, 1936. Rivers and Scott.<sup>2</sup>

5 Smadel, J. E., Baird, R. D., and Wall, M. J. Complement-Fixation in Infections with the Virus of Lymphocytic Choriomeningitis, *Proc. Soc. Exper. Biol. & Med.* **40** 71-73 (Jan.) 1939. Smadel, J. E., Wall, M. J., and Baird, R. D. A Soluble Antigen of Lymphocytic Choriomeningitis. II. Characteristics of the Antigen and Its Use in Precipitin Reactions, *J. Exper. Med.* **71** 43-53 (Jan.) 1940.

6 Obtained through Dr. Joseph Zichis, of the Illinois Department of Public Health.

On Jan 1, 1942 (two hundred and thirty-two days after the initial attack) there was a strong concentration of neutralizing antibodies in the patient's serum against the newly isolated, J P, A M and W E (Rivers) strains of choriomeningitis virus. At this time the complement-fixing antibody titer was 1/40.

#### ANTIBODY STUDIES OF POOLED NORMAL ADULT HUMAN SERUM

Because of the patient's favorable response to pooled normal adult serum,<sup>9</sup> we considered it desirable to test several pools of serum for the presence of lymphocytic choriomeningitis antibodies. Unfortunately, the pooled serum administered to the patient was not available for study. For this reason several other pools of serum selected at random were tested. The results are given in table 3. Of 12 serum pools tested, 3 proved to contain neutralizing

TABLE 3—*Lymphocytic Choriomeningitis Neutralizing and Complement-Fixing Antibodies in Pooled Normal Adult Human Serum*

Pool No	Neutralizing Antibodies	Complement-Fixing Antibodies
204	0	0
209	0	0
215	+	Anticomplementary
220	0	0
522	0	0
523	0	0
524	0	0
525	+	0
526	0	0
527	+	0
528	0	0
529	0	0

antibodies, inactivating at least 100 minimal lethal doses of the J P strain of choriomeningitis virus. One pool was anticomplementary, the remaining eleven pools contained no complement-fixing antibodies.

#### COMMENT

There can be no question, from the isolation of the virus in both episodes of the illness and from the subsequent development of virus-neutralizing substances, that this patient suffered an attack and recurrence of lymphocytic choriomeningitis. Armstrong<sup>10</sup> has stated that this ailment in man presents a remarkably variable clinical picture—a meningeal, an encephalomyelitic and a grippal or non-nervous-system type. Despite this consideration, it is extremely difficult to say that all the manifestations in this instance were due to the disease process. The clinical picture at times was so strongly suggestive of hysteria that only few of us entertained the thought that the clinical picture was not a pure hysteria. Naturally, after the virus and immunologic studies we were convinced that the patient had suffered an attack of a real infection. The question may still be raised, however, whether all the symptoms and findings were caused entirely by the infectious process. It is possible that some of the symptoms were due to a hysterical component.

In addition to the unusual clinical manifestations, there were other unique aspects in this case. The patient's temperature was practically normal throughout the illness. Examinations of the spinal fluid disclosed no particular change.

7 Obtained through Dr Charles Armstrong, of the National Institute of Health.

8 Howitt, B F. Viruses of Equine and of St. Louis Encephalitis in Relationship to Human Infections in California, 1937-1938, *Am J Pub Health* **29** 1083-1097 (Oct) 1939.

9 Each pool of normal adult human serum consists of approximately 4 liters of serum obtained from 18 to 20 healthy adult urban donors.

10 Armstrong, C. Some Recent Research in the Field of Neurotropic Viruses with Especial Reference to Lymphocytic Choriomeningitis and Herpes Simplex, *Mil Surgeon* **91**, 129-146 (Aug) 1942.

Of particular interest was the absence of pleocytosis in the spinal fluid. In a previous publication<sup>1b</sup> we have pointed out that the spinal fluid may be normal in the acute stage of lymphocytic choriomeningitis and that only virus and immunologic studies can confirm or rule out the presence of this disease.

The demonstration of neutralizing antibodies for the virus of St. Louis encephalitis was an incidental finding of considerable interest in view of the history that the patient had lived in El Cajon, San Diego County, Calif., and had suffered from a rather obscure illness five years previously. In view of the demonstration of antibodies and the fact that this disease is endemic in California,<sup>11</sup> it is not unlikely that this illness had been a mild attack of St. Louis encephalitis.

Pooled normal adult human serum was administered on an empiric basis, since we felt that the illness might be due to an infection and we hoped that the serum might contain neutralizing antibodies which would be of benefit. The rather spectacular response to the first administration of serum seemed to strengthen the theory that the condition was hysteria. Serum therapy was therefore withheld during the recrudescence and was finally administered only as a last resort measure and without much hope of any effect. We were greatly surprised to witness a response to the second injection of serum comparable to that seen with the initial attack.

In an attempt to explain the improvement coincidental with administration of serum studies were carried out on 12 random pools of normal adult human serum. Unfortunately, we did not save serum from the pools used in treating the patient. The results of titration of these random pools are summarized in table 3 and reveal that 3, or 25 per cent, contained neutralizing antibodies against the choriomeningitis virus. This result is not unexpected, in view of Armstrong's finding that approximately 11 per cent of 2,000 serums from the general population contained such antibodies.<sup>12</sup>

We shall not attempt to draw any conclusions from the use of serum in this single case. Nevertheless, it is a fact that with both episodes of this disease the patient, when appearing in a critical condition, improved markedly promptly after the administration of large amounts of pooled normal adult serum which may have contained neutralizing antibodies for the virus of choriomeningitis. Obviously a great deal of work and study must be carried out before any definite conclusions can be reached.

#### SUMMARY

In a case of recurrent lymphocytic choriomeningitis the virus was isolated from spinal fluid obtained during the initial attack and again during the recrudescence. The patient subsequently had a strong concentration of both neutralizing and complement-fixing antibodies for the choriomeningitis virus in her blood serum. The case showed several unusual clinical features, especially the clinical picture of an encephalomyelitis associated with absence of pleocytosis or other abnormal findings in the spinal fluid and an essentially afebrile course. Administration of pooled normal adult human serum in large amounts appeared effective in the control of both the first attack and the recrudescence of the disease. The presence of neutralizing antibodies against the virus of lymphocytic choriomeningitis was demonstrated in 3 of 12 random pools of normal adult human serum, while no complement-fixing antibodies were detected.

11 Howitt, B. F. Human Equine Encephalomyelitis and St. Louis Encephalitis in California, 1939-1941, *Am J Pub Health* **32** 503-515 (May) 1942.

12 Armstrong, C. Studies on Choriomeningitis and Poliomyelitis, in *Harvey Lectures*, series 36, 1940-1941, Lancaster, Pa., Science Press Printing Company, 1941, pp. 39-65.

# EFFECT OF ROENTGEN THERAPY ON THE HEART

## A CLINICAL STUDY

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The modern treatment of cancer is a group project, requiring the close cooperation of the surgeon, the radiologist and the internist. Among the more important problems with which the internist must deal are the effects of radiant energy on vital structures, such as the gastrointestinal system, the kidneys, the lungs and the heart, in patients who are receiving or have received radiation therapy. The purpose of this paper is to report these effects on the cardiovascular system as they have been observed clinically.

This paper is the fourth in a series from the medical service of Memorial Hospital on the effect of radiation therapy on the heart and the lungs. The first two<sup>1</sup> dealt with the immediate and the late effects of high voltage roentgen rays on the hearts of adult rats. Work now in progress will supplement these reports and is concerned with the pathologic physiology of chronic radiation pleuropulmonitis. A preliminary report on this phase of the subject has already been given.<sup>2</sup>

## LITERATURE

A review of the literature shows many reports concerning the effect of roentgen radiation on the hearts of laboratory animals. Warren and Whipple and others<sup>3</sup> failed to find evidence of muscle change macroscopically or microscopically when the heart was subjected to varying doses of roentgen rays. On the other hand, Davis<sup>4</sup> and Hartman and associates<sup>5</sup> provoked alteration of the myocardium by irradiation of the heart. Domagk<sup>6</sup> recorded instances of myocardial fibrosis in

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From the Medical Department, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York

1 Leach, J. E., and Sugiura, K. (a) The Effect of High Voltage Roentgen Rays on the Hearts of Adult Rats, *Am J Roentgenol* **45** 414-425 (March) 1941, (b) The Late Effect of High Voltage X-Rays on the Heart of Adult Rats, *ibid*, to be published.

2 Leach, J. E., Farrow, J. H., Wawro, N. W., and Foote, F. W., Jr. Fibrosis of the Lung Following X-Radiation for Breast Cancer, *Am J Roentgenol*, to be published.

3 Warren, S. L., and Whipple, G. H. Roentgen Ray Intoxication. Unit Dose Over Thorax Negative—Over Abdomen Lethal, Epithelium of Small Intestine Sensitive to X-Rays, *J Exper Med* **35** 187-203 (Feb) 1922. Gordon, B., Strong, G. F., and Emery, E. S., Jr. Effect of Direct Radiation Over Precordium on Heart Size—Heart Mechanism and Myocardium of Rabbits, *Am J Roentgenol* **11** 328-330 (April) 1924. Warthin, A. S., and Pohle, E. A. Effect of Roentgen Rays on the Heart, Microscopic Changes in Heart Muscle of Rats and Rabbits Following Single Exposure, *J A M A* **89** 1825-1829 (Nov 26) 1927, Effect of Roentgen Rays on the Heart. Microscopic Changes in Heart Muscles of Rats and of Rabbits Following a Series of Exposure, *Arch Int Med* **43** 15-34 (Jan) 1929.

4 Davis, K. S. Intrathoracic Changes Following X-Ray Treatment. Clinical and Experimental Study, *Radiology* **3** 301-322 (Oct) 1924.

5 Hartman, F. W., Bolliger, A., Doub, H. F., and Smith, F. J. Heart Lesions Produced by Deep X-Rays. Experimental and Clinical Study, *Bull Johns Hopkins Hosp* **41** 36-61 (July) 1927.

6 Domagk, G. Gewebsveränderung nach Röntgenbestrahlungen, *Ergebn d inn Med u Kinderh* **33** 1-62, 1928.

animals that survived irradiation of the entire body Leach and Sugiura<sup>1a</sup> found that at least 10,000 r (measured in air) delivered through a precordial port was required to cause capillary hemorrhage and round cell infiltration in the heart muscle The endocardium and the pericardium resisted single doses up to and including 20,000 r In another group of animals, killed seven months or more after treatment, myocardial fibrosis was not caused by doses up to and including 7,500 r<sup>1b</sup>

Clinical observations of the effects of roentgen radiation on the heart are scant Thibaudeau and Mattick<sup>7</sup> reported postmortem observations on patients who died from cancer and who had received radiation to organs adjacent to the heart They concluded that cardiac damage might result from roentgen therapy Gendreau<sup>8</sup> noted the frequent occurrence of cardiac arrhythmia of all types in patients while they were undergoing roentgen irradiation of different regions of the body, including the thorax Desjardins<sup>9</sup> carefully reviewed all of the literature up until 1932 and came to the conclusion that roentgen rays as used clinically at that time (1932) would not cause cardiac damage

#### SELECTION OF PATIENTS

This study presented some difficulties In the choice of patients those required were the ones whose neoplastic disease was not so far advanced that they were likely to die from its effect before adequate follow-up examinations could be made The ideal patient was one who had a localized cancer, who was in good general condition and who was to receive roentgen therapy alone In many patients of this type, however, surgical procedures had to be added to the roentgen therapy, and in others distant metastasis developed, with resultant cachexia Some of the patients were lost track of or died elsewhere, so that adequate postmortem examination was impossible

Eighty-five patients were selected They included patients of all ages (except children) and of varied occupations The great majority fell into the late middle and senile age groups for the obvious reason that cancer is more prevalent in persons of such age groups There were patients with normal hearts and patients with various types of heart disease, particularly the arteriosclerotic type

#### METHOD OF STUDY

Each patient first received a general survey, which included a complete history and physical examination Each was then examined with special reference to the neoplastic disease for which he originally sought treatment The second examination varied from a local examination and biopsy for histologic diagnosis to extensive roentgenographic and endoscopic studies With some patients an aspiration biopsy was done to establish the diagnosis of tumor None of these procedures caused any change in the local neoplastic process or had any sustained effect on the general well-being of the patient A third examination consisted of (1) a history with particular reference to the cardiovascular system, (2) a physical examination, (3) a teleroentgen or fluoroscopic examination of the chest and heart and (4) an electrocardiographic examination

At intervals which varied somewhat with the type of treatment they were to receive, the patients were reexamined and further roentgenograms of the chest and electrocardiograms were made The time of the second examination was made to coincide as closely as possible with the height of the reaction which resulted from the first course of roentgen therapy Further examinations were made at intervals up to three months as indicated by the patient's treatment, symptoms and general health If symptoms or signs of cardiac failure occurred in a patient before, during or after therapy, he was seen at much shorter intervals If, on the other hand, a patient was obviously doing well, he was seen at the end of three months The follow-up period for some of the patients was only a few months, since they died early in the course of

7 Thibaudeau, A. A., and Mattick, W. L. Histological Findings in Hearts Which Have Been Exposed to Radiation in Course of Treatment of Adjacent Organs, *J. Cancer Research* **13** 251-259 (Oct.) 1929

8 Gendreau, J. E. Far Reaching Effects of Gamma Rays and Short X-Rays upon Human Heart, *Ann. Surg.* **93** 476-480 (Jan.) 1931

9 Desjardins, A. U. Action of Roentgen Rays and Radium on Heart and Lungs. Experimental Data and Clinical Radiotherapy, *Am. J. Roentgenol.* **27** 149 (Jan.), 303 (Feb.), 477 (March) 1932, **28** 127-143 (July), 271-292 (Aug.), 421-436 (Sept.), 567-578 (Oct.), 699-720 (Nov.), 843-858 (Dec.) 1932



then care or were lost to other institutions for a variety of reasons. Other patients have been followed for over three years.

The electrocardiograms were taken both with an amplifying and with a galvanometer type of machine. All were taken with the subject in the supine position, and the standard limb leads were used. Precordial leads were used with some patients but not with patients in group III (see next section) because of the frequent change in the position of the heart in the thorax following chronic radiation pleuropulmonitis.

#### GROUPING OF PATIENTS

For purposes of comparison, the patients have been placed in three groups, depending on the location of the original tumor.

Group 1 consists of patients with cancer of the head, neck, cervix uteri or rectum. While these are dissimilar diseases, for this study they have certain features in common. The treatment was largely roentgen irradiation of the tumor and radon seed implantation, and there was a minimum of surgical intervention. Most important, the upper portion of the abdomen and the chest were not irradiated.

Group 2 is a miscellaneous collection of patients who had malignant lymphoma or teratoma. These patients are grouped together because the intrathoracic structures, as well as other parts of the body, received radiation.

Group 3 includes patients with cancer of the breast, lung, esophagus or the cardiac end of the stomach, as well as 1 patient with tuberculosis of the mediastinal lymph nodes. These are placed together because the thorax was the chief region treated and the rest of the body did not receive radiation.

#### COMPARISON OF RADIATION THERAPY AND ADVERSE EFFECTS IN THE THREE GROUPS

*Group 1*—This group is made up of patients with cancer in the following locations:

	Patients
Buccal mucous membrane	1
Floor of the mouth	1
Tongue	2
Tonsil	1
Rhinopharynx	1
Extrinsic larynx	3
Cervix uteri	6
Rectum	5
Sigmoid portion of the colon	1

The group includes 14 men and 7 women, ranging in age from 40 to 82 years. The majority were from 50 to 70 years of age. Eleven patients had no evidence of heart disease. Ten had mild to moderate forms of arteriosclerotic heart disease with variable degrees of hypertension and myocardial fibrosis, with and without mitral incompetency and aortic sclerosis. All had regular sinus rhythm, and only 2 had less than class I functional capacity. These patients had class II functional capacity.

In the patients with cancer of the head and neck the roentgen therapy consisted of a course of radiation therapy through one or more portals. At the height of the ensuing reaction, three to six weeks after starting therapy, gold radon seeds were frequently implanted to supplement the roentgen ray effect. In these patients there usually developed severe mucositis in the treated region with variable degrees of dysphagia or trismus or both. These symptoms were so severe in some patients



TABLE 1—Data on Patients in Group 1

Diagnosis	Name and Treatment *	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Weight Change from Normal †	Dys phagia ‡	Cardiac Symptoms	Comment
1 Cancer of buccal mucous membrane	T T 5/16 6/14, 4,600 r left cheek 6/14, 930 mc in lesion 6/28, 406 mc in lesion 9/2, 4,800 r to node left side of neck 9/20, 1520 mc in node left side of neck 12/13, 609 mc in node left side of neck	43	M	Essential hypertension	5/16/38, 158/100 6/10/38, 164/100 9/6/38, 160/100 12/13/38, 164/102 3/13/39, 172/100	0 0 0 0 0	0 0 0 0 0	None	
2 Cancer of floor of mouth	T B 4/18-5/17, 7,800 r to lesion through oral cone 5/17, 1014 mc in lesion 5/24, 1055 mc in node in neck	51	M	Normal heart	4/12/38, 120/92 5/24/38, 114/90 8/11/38, 110/85 12/15/40, 114/80	0 — 0 0	0 — 0 0	None	
3 Cancer of tongue	J H 5/26-6/9, 3,000 r by 2 portals to lesion 3,000 r to node in neck 8/9 8/23, 3,300 r by 2 portals to lesion	75	M	1 Hypertension, arteriosclerosis 2 Enlargement of heart, mitral incompetency, aortic sclerosis 3 Regular sinus rhythm 4 1 functional capacity I	5/23/38, 170/90 7/2/38, 146/92 10/27/38, 170/100 1/6/39, 158/98 4/20/39, 170/100	0 — 0 0 0	0 — 0 0 0	None	
4 Cancer of tongue	A S 5/3, 5,000 r to lesion 5/27, 916 mc in lesion	61	M	1 Hypertension, arteriosclerosis, "labilis" 2 Myocardial fibrosis 3 Regular sinus rhythm 4 Functional capacity I	4/20/38, 180/100 5/26/38, 163/100 8/25/38, 152/00 11/21/38, 118/96 3/6/39, 162/81 7/18/39 1/1/40, 180/100	0 — — + — 0 Normal	0 — 0 0 0 0 0	None	
5 Cancer of rhinopharynx	D D P 4/18-5/6, 4,200 r by 2 portals through cheeks 4,200 r left upper part of neck 5,600 r right upper part of neck	41	M	1 Essential hypertension 2 Enlarged heart 3 Regular sinus rhythm 4 Functional capacity I	4/18/39, 150/120 5/6/39, 110/100	0 —	0 —	None	
6 Cancer of tonsil	G K 5/26-6/27, 4,000 r to lesion through oral cone 4,500 r left side of neck 7/22, 3300 mc right carotid node 7/22, 623 mc anterior tonsillar pillar 7/28, 2201 mc left carotid node	66	M	1 Arteriosclerosis, hypertension 2 Normal heart	1/22/38, 162/82 7/12/38, 120/92 10/7/38, 110/90 11/15/38, 128/00	0 — — +	0 — — 0	None	
7 Extrinsic cancer of larynx	T H 5/31 7/1, 4,200 r each side of larynx	65	M	1 Hypertension, arteriosclerosis 2 Myocardial fibrosis 3 Regular sinus rhythm 4 Functional capacity I	5/31/38, 180/100 7/1/38, 120/82 10/26/38, 200/110 1/30/39, 180/100 4/27/39, 200/100 1/30/40 10/10/40, 160/100	0 — + — + — 0	0 ++ ++ 0 0 0 0	↑ after dyspnea unchanged after radiation reaction subsided	Progressive lowering of T waves up to Jan uary 1940, in October 1940 T waves had nor mal voltage marked dyspnea and cough at height of radiation reaction
8 Extrinsic cancer of larynx	J M 4/12-5/17, 5,200 r each side of larynx 3,700 r postcervical 7/21 8/15, 1,800 r left side of neck	18	M	Normal heart	4/1/38, 112/70 5/12/38, 110/72 9/2/38, 114/72	0 — —	++ ++ ++	None	Marked dyspnea and cough at height of radiation reaction
9 Extrinsic cancer of larynx	J L 3,600 r each side of larynx 30 mc right carotid bulb node	64	M	1 Arteriosclerosis 2 Myocardial fibrosis, coronary sclerosis 3 Regular sinus rhythm with anginal symptoms 4 1 functional capacity I	1/1/38, 160/90 5/6/38, 110/46	0 0	0 ++	Died, probably coronary occlusion	Marked dyspnea and cough at height of radiation reaction

10	Cancer of sigmoid	Mrs H Radium pack	65	F	1 Arteriosclerosis 2 Normal heart	5/16/38 4/21/38, 130/ 82	—	None
11	Cancer of cervix uteri, League of Nations class III	F D 4/12, 750 r by 6 pelvic portals 5/16, 757 mc hr by vaginal applicator 5/17, 76 mc hr cervical tandem 10/26, 174 mc right parametria	47	F	1 Hypertension 2 Normal heart	4/ 4/38, 160/100 4/21/38, 130/ 82 10/ 3/38, 170/110 4/ 3/39, 130/ 90	— — 0 —	Progressive lowering of T waves as cachexia supervened
12	Cancer of cervix uteri	O N 1,000 r by 6 pelvic portals 1,000 mc hr by vaginal applicator 2,700 mc hr cervical tandem	60	F	Normal heart	4/21/38, 150/ 92 5/ 5/38, 146/ 92	0 —	None
13	Cancer of cervix uteri, League of Nations class III	G L 200 r by 6 pelvic portals 1,000 mc hr cervical bomb 3,000 mc hr cervical tandem	73	F	1 Hypertension, arteriosclerosis 2 Enlargement of heart, myo cardial fibrosis 3 Regular sinus rhythm 4 Functional capacity I	5/23/38, 170/ 90 7/ 5/38, 148/ 82 10/11/38, 180/100 3/13/39, 163/100 4/17/40, 172/100	0 0 0 0	Exertion dyspnea unchanged
14	Cancer of cervix uteri	J S 7/12 7/19, 750 r by 6 pelvic portals 8/9/38, 3,000 mc hr tandem	82	F	1 Hypertension, arteriosclerosis 2 Enlargement of heart, myo cardial fibrosis 3 Regular sinus rhythm 4 Functional capacity II	7/11/38, 163/112 8/15/38, 150/100 12/15/38, 160/120 4/10/39, 150/ 90	0 0 — —	Nocturnal dyspnea T waves increased at height of therapy, T waves decreased with digitalization
15	Cancer of cervix uteri	M M 8/10-9/3, 1,700 r by 6 pelvic portals 10/3, 1,000 mc hr cervical bomb 10/4, 3,000 mc hr cervical tandem	40	F	Normal heart	8/ 1/38, 132/ 80 9/24/38, 104/ 78 11/ 3/38, 117/ 80	0 — —	None
16	Cancer of cervix uteri	E B 1,700 r by 4 pelvic portals 8/33, 1,000 mc hr cervical bomb 3,000 mc hr cervical tandem	51	F	Normal heart	6/ 8/38, 138/ 80 — 138/ 90	0 — 0	None
17	Cancer of rectum	H B 900 r by 4 pelvic portals	57	M	1 Burger's disease 2 Coronary sclerosis 3 Regular sinus rhythm with anginal symptoms 4 Functional capacity II	11/10/38, 160/ 92 12/28/38, 162/ 98	0 0	Anginal syndrome unchanged
18	Cancer of rectum	N S 900 r by 6 pelvic portals 700 r perineal portal 4 mc hr rectal applicator	67	M	1 Arteriosclerosis 2 Normal heart	4/26/38, 160/100 6/ 2/38, 150/ 92 8/16/38, 140/ 82	0 — —	T waves progressively lowered as cachexia supervened
19	Cancer of rectum	I S 450 r by 4 pelvic portals 10 mc hr rectal applicator	70	M	Normal heart	5/10/38, 150/ 82 5/31/38, 142/ 80 9/29/38, 140/ 82	0 — —	T waves progressively lowered with cachexia
20	Cancer of rectum	D B 900 r to perineum 1,200 r by 2 posterior pelvic portals 2,000 mc hr rectal applicator	82	M	1 Arteriosclerosis 2 Myocardial fibrosis 3 Regular sinus rhythm with premature ventricular contraction 4 Functional capacity II	6/ 9/38, 148/ 80 6/30/38, 146/ 60	0 —	Exertion dyspnea unchanged
21	Cancer of rectum	M W 900 r by 7 pelvic portals 3,200 mc hr rectal applicator	54	M	1 Hypertension, arteriosclerosis, obesity 2 Enlargement of heart, myo cardial fibrosis 3 Regular sinus rhythm with anginal symptoms 4 Functional capacity I	4/18/38, 130/110 5/10/38, 142/ 82 9/29/38, 145/ 90 12/ 1/38, 152/ 98 12/15/40, 160/110	0 — — + +	Progressive T wave voltages progressively lowered as patient's cardiac symptoms increase anginal pain, in mild failure on two occasions

\* In column headed "Name and Treatment" r means roentgen units, mc, millicuries of radium, mc hr, millicurie hours of radium therapy. Such an expression as "3,000 r by 2 portals" means that the stated dose was given through each portal.  
† In the column headed "Weight" the sign — means that the loss of weight was moderate, — — —, loss of weight was marked, +, patient was regaining lost weight.  
§ In column headed "Dysphagia" or "Toxemia" or "Anemia" the sign + means mild ++, moderate, +++ marked.

that liquids were the only form of nourishment for a time. Loss of weight was marked in some patients. Dyspnea, persistent cough, aspiration and obstructive tracheobronchitis due to laryngeal and pharyngeal edema, infection of the tumor and faulty deglutition frequently developed in addition to dysphagia in those patients with radiation directed to the larynx and the hypopharynx.

Patients with cancer of the cervix uteri usually had a pelvic cycle up to 1,800 r through four pelvic portals, followed in six weeks by a cervical tandem of 3,000 to 3,600 milligram hours of radium. The latter treatment had to be delayed in some instances because of cervical stenosis and secondary pyometra. Moderate radiation nausea and vomiting which interfered with nutrition and maintenance of weight developed in some patients. Local infection of the tumor, uterine infection and secondary anemia were not uncommon. The radiation reaction and bleeding tended to decrease the patients' strength.

The patients with rectal cancer received an average dose of 950 r by four pelvic portals plus local radium therapy by means of a special applicator. Many after treatment experienced severe gastrointestinal symptoms with anorexia, abdominal cramps, diarrhea and marked rectal tenesmus. These factors often interfered with adequate rest and nutrition.

Loss of weight was most marked in the group with cancer of the head and neck and was present to a lesser extent in the group with pelvic cancer. This was due to the marked dysphagia usually present at the height of the radiation reaction in the patients with cancer of the head and neck and to the longer period of active treatment which they underwent.

An appreciable drop in blood pressure was noted in only 4 patients with pelvic neoplasms whereas 6 of the 9 patients with cancer of the head and neck had a moderate to marked decrease of blood pressure. In the latter this decrease was roughly proportional to the loss of weight. In the group with pelvic cancers some of the patients losing weight had decreased blood pressure and some did not.

The fall in the blood pressure of patients receiving roentgen therapy (fig 1) has been attributed by some investigators to absorption of split protein (histamine-like) substances secondary to destruction of tissue. This may be true, but deficient intake of food with the attendant loss of weight would seem to play a more important role in these patients. This change in blood pressure was not necessarily dependent on the presence of antecedent heart disease or previous hypertension. As the reaction subsided, many of the patients tended to regain their former level of blood pressure.

The serial electrocardiograms were interesting but somewhat confusing. The voltage of P waves and the QRS complexes varied to a moderate degree. There was no variation of the auriculoventricular conduction times. The voltage of the T waves also varied in some. These changes were not proportional to previous cardiac disease, alteration of the blood pressure, loss of weight, toxemia, severity of the radiation reaction at its height or to type of neoplastic disease present. Probably the changes noted depended on the interplay of all these factors, some more important than others, but too complicated to permit accurate analysis. One point was especially striking. This was the gradual lowering of the voltage of all the waves, especially of the T waves, in patients who were suffering from cachexia due to widespread cancer. Simon and Baum<sup>10</sup> noted similar T wave changes.

10 Simon, S., and Baum, F. Electrocardiographic Studies in Pulmonary Tuberculosis. Preliminary Report on Two Hundred and Fifty Cases, *Ann Rev Tuberc* **17** 159-181 (Feb) 1928.

in patients who were suffering from terminal pulmonary tuberculosis. Their explanation that this represented a result of progressive depression of the myocardium due to toxemia probably applies to these patients with terminal cancer.

Outstanding cardiac complications following therapy were observed in 2 of the 21 patients. One was a man with cancer of the larynx who had symptoms of coronary sclerosis with angina of effort and who had had cardiac failure two years before, for which he had been treated by his family physician. He received fairly heavy roentgen radiation to his larynx. At the height of the reaction he complained of incessant cough with expectoration and increasing dyspnea with effort, due to the marked edema of the larynx and obstructive tracheobronchitis. He did not complain of any increased cardiac pain at the time. Three months later he died suddenly at home as a result of a heart attack, presumably a coronary occlusion.

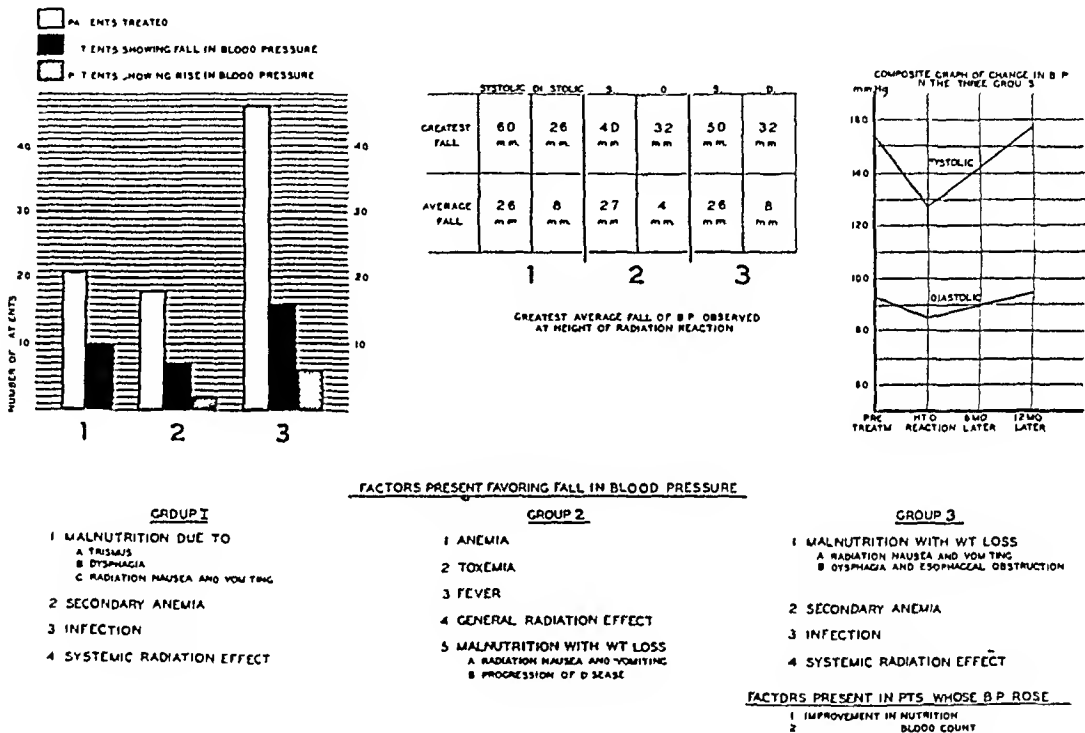


Fig 1—The effect of high voltage roentgen therapy on the blood pressure of 85 patients treated for cancer. The presence of hypertension or heart disease or both did not influence these results. Group 1 includes 21 patients with cancer of the head, neck, cervix uteri or rectum, roentgen radiation was directed to these areas, but the thorax was not irradiated. Group 2 includes 18 patients with lymphoma or teratoma, roentgen therapy was directed to various parts of the body including the thorax. Group 3 includes 42 patients with cancer of the breast, lung, esophagus or cardiac end of the stomach, 3 with other types of neoplastic diseases and 1 with tuberculosis of the mediastinal lymph nodes, only the thorax was irradiated.

The second patient, a woman of 82 years with a cervical cancer, had hypertension with an enlarged heart and mitral incompetency for some years prior to treatment. An electrocardiogram made before treatment showed auricular premature systoles. She had relatively little difficulty during the time she received roentgen and radium tandem therapy. Five months later she complained of palpitation and dyspnea and on examination was found to have an increased degree of hypertension and auricular fibrillation with a rapid ventricular rate. At the same visit she was found to have a large pyometra.

After careful consideration one cannot attribute the coronary occlusion in the one patient and the auricular fibrillation in the other patient to roentgen therapy *per se*. While it is true that in the man the laryngeal edema, tracheobronchitis and incessant cough may have helped to precipitate the coronary occlusion, a nonspecific infection of the respiratory tract could have conceivably produced the same result. In the woman the pyometra, toxemia and anemia possibly played a part in precipitating the arrhythmia, but these conditions are not necessarily secondary to roentgen therapy and can arise in the course of various pelvic diseases.

It would be well to mention at this point 3 other patients not included in group 1 who have been observed over the past two years. They had carcinoma of the floor of the mouth, the tongue and the hypopharynx, respectively. The first had a normal cardiovascular system, the second had generalized arteriosclerosis with myocardial fibrosis, and the third a mild degree of generalized arteriosclerosis without demonstrable heart disease. Oddly enough, all the primary lesions were on the left side, and all the patients had bulky metastases to the upper left cervical nodes, i. e., those intimately associated with the bifurcation of the carotid artery. Two had, in addition to local metastases, a necrotic, sloughing primary lesion with an inflammatory reaction in the metastatic nodes.

The symptoms and signs exhibited by them were all similar and were as follows. At the height of their reaction to radiation, when there was considerable edema of the tissues of the lateral side of the neck, the patients began to have attacks of syncope preceded by marked pallor, sweating, feeble slow pulse and almost inaudible heart sounds. These attacks lasted from thirty seconds to several minutes and were followed by a period of weakness and some apprehension. One patient fainted five times in one hour after examination in the follow-up clinic. None had fainted before.

On observing these patients the following points were noted. The pulse first became weak and slowed rather abruptly until the rate was 40 to 50 per minute with an occasional premature systole. The systolic blood pressure, which had been within normal limits at first, fell to 60 to 80 mm. of mercury, and the patients became extremely pale and fainted. The pulse continued to be slow, and 2 patients made slightly spasmodic movements of the arms and legs during syncope. The attacks lasted variable times, and the patients frequently recovered before any stimulants were given. Of 2 patients tested by pressing over the involved cervical nodes, the first had an abrupt slowing of the pulse and the second complained of vertigo.

One must conclude from the type of attack and the presence of infected metastatically involved cervical nodes that these were instances of carotid sinus syncope.

These patients responded quickly to large doses of atropine. The atropine effect was maintained for a few days, with tincture of belladonna administered by mouth until the infection subsided. The attacks ceased and did not recur. One patient continued to have the attacks for a week despite the added use of ephedrine sulfate  $\frac{3}{4}$  grain (0.045 Gm.) given four times daily by mouth.

No attacks of this type have been observed in patients who had radical cervical dissections, in many of whom the vagus nerve was sacrificed. None has been observed in those patients in whom the vagus nerve was possibly destroyed by implantation of radon seeds in metastatically involved nodes in the neck. When the vagus nerve is severed or destroyed, the contralateral nerve is sufficient to carry the normal regulatory impulse to and from the heart and aorta and the contralateral sinus.

*Group 2* —The second group is made up of patients with the following types of cancer

	Patients
Brill-Symmer disease (giant follicular lymphoma)	1
Hodgkin's disease	10
Lymphosarcoma	2
Teratoma testis with widespread metastases	2
Lymphatic leukemia	3

These patients are grouped together because of the anatomic similarity of all these diseases except teratoma and because their treatment was directed to widely scattered regions in the body, including the thorax. The usual practice is to treat patients with these diseases less vigorously than patients with epidermoid carcinoma or adenocarcinoma. However, the 2 patients with teratoma were given heavy doses of radiation over an extended period. The ages ranged from 22 to 71 years, and there were 12 men and 6 women. Five patients had heart disease, in 2 it was rheumatic in origin, and in 3 it was secondary to hypertension and arteriosclerosis. These patients all had class I functional capacity with the exception of patient 17 (table 2), who had class II functional capacity.

Treatment of patients in this group differed widely. Roentgen radiation was given in doses totaling from 400 to 2,000 r to single portals and these were repeated or not, depending on the course of the individual patient's disease. The 2 patients with lymphosarcoma were treated more vigorously than the 10 with Hodgkin's disease. The 3 with lymphatic leukemia each received 75 r in the Heublein unit (irradiation of the whole body).

A drop in blood pressure was observed in 7 patients, 9 others had essentially no change in blood pressure and in 2 patients the blood pressure was higher at the end of treatment than it had been on admission to the clinic (fig 1). While there was no apparent direct relation between the decrease of the blood pressure in the 7 patients and anemia, toxemia, fever and general radiation effect, all or some of these factors were present and undoubtedly played major roles in lowering the blood pressure after roentgen therapy. The blood pressure continued to fall in some of the patients as the disease became generalized.

Loss of weight was not a prominent factor in the patients of this group. In fact, they either maintained their admission weight or gained during the time they received the first cycle of roentgen therapy. This was particularly true in those with Hodgkin's disease who were toxic and anemic before treatment. Some had fever before treatment was started. Later on, as the disease progressed, loss of weight was marked in some.

The serial electrocardiograms in this group were interesting. The P wave voltage and the PR and QRS intervals were unchanged. There were slight changes in the QRS voltage in all patients except 1 in whom the changes were marked. Changes in T wave voltage were common and varied widely. In some patients all the T waves were increased, in others only  $T_1$ ,  $T_2$  or  $T_3$  was increased. However, the increases did not follow any pattern. One patient with advanced Hodgkin's disease who was very cachectic showed all the T waves lowered as in the patients with generalized carcinomatosis in group 1. In group 2 the generalized nature of the neoplastic disease, the fever, the anemia, the toxemia and the depressing effect of the radiation itself possibly contributed all or in part to the electrocardiographic changes. One could not link these changes with heart disease secondary to the roentgen therapy.

TABLE 2—Data on Patients in Group 2 +

Diagnosis	Name and Treatment	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Weight Change	Toxemia	Anemia	Comment
1 Hodgkin's disease	L W 5/27, 2,000 r by 2, anterior and posterior mediastinum 10/4, 700 r by 4 directed at cervix	56	F	Normal heart	5/26/38, 122/70 6/22/38, 108/80 7/21/38	— — 0	++ 0 0	++ 0 0	
2 Hodgkin's disease	S Y 900 r by 2, anterior and posterior mediastinum	25	F	Normal heart	2/17/39, 112/80 4/25/38, 120/80 5/12/38, 106/70 7/14/38, 104/88	— — — —	++ 0 ++ ++	0 0 ++ ++	Cachectic, pleural effusion on left 7/14/38
3 Hodgkin's disease	S M 4/2/39, 1,200 r by 2, right and left side of neck 1,200 r by 2, anterior and posterior mediastinum 9/26, 800 r right supraclavicular space	34	F	1 Hypertension and obesity, normal heart	3/25/39, 100/112 5/4/39, 120/80 12/25/39, 120/90	0 — —	++ 0 0	++ ++ ++	
4 Hodgkin's disease	D N Dec 1938 to March 1939 600 r by 2, left side mediastinum, anterior and posterior 900 r by 2, upper mediastinum, anterior and posterior 1,000 r by 2, left upper chest, anterior and posterior 1,000 r supraclavicular space	38	F	Normal heart	10/25/38, 102/78 1/20/39 112/80	— —	++ ++	++ ++	T waves decreased in volt age as cachexia super vened
5 Hodgkin's disease	W S 3,000 r by 2, right side upper neck 4,800 r right side lower neck	71	F	1 Hypertension, arteriosclerosis 2 Enlargement of heart, mitral incompetency 3 Regular sinus rhythm 4 Functional capacity I	1/29/38, 170/100 5/19/38, 210/100	— —	— 0	— —	
6 Hodgkin's disease	D I 4/6/27, 1,800 r by 2, mediastinum, anterior and posterior	54	M	Normal heart	4/7/38, 112/80 7/5/38, 114/84	0	++ 0	— —	
7 Hodgkin's disease	T O 550 r right side upper neck 800 r left side upper neck 550 r right side lower neck 900 r left side lower neck 550 r right axilla 900 r left axilla	53	M	Heart normal	4/27/38, 110/82 7/10/38, 114/82	— 0	++ 0	++ ++	
8 Hodgkin's disease	L B July 1938, 1,000 r neck October, 900 r by 2, mediastinum, anterior and posterior December, 50 r Huebner unit February April 1,000 r abdomen	44	M	Normal heart	10/11/38, 112/80 11/10/38, 118/92 12/25/38, 124/80 12/27/38, 96/82 1/17/39, 120/80 4/28/39, 122/88	— 0 — — — —	++ 0 0 0 ++ ++	++ ++ ++ ++ ++ ++	

9	Hodgkin's disease	F S	50	M	1 Hypertension 2 Cardiac enlargement 3 Regular sinus rhythm 4 Functional capacity I	6/10/38, 180/100 7/29/38, 142/106 12/15/38, 140/90 3/9/39, 145/95	— + + —	+ 0 0 0	+ + 0 +
10	Lympho sarcoma	Dr F 10/17 11/12/38, element pack 30,000 mg hr upper abdomen 11/2 11/12/38 600 r by 2, mediastinum, anterior and posterior 10/17-11/12/38, 600 r by 2, right and left axilla, 900 r left side neck, 600 r left supraclavicular space 6/14/40, 8 abdominal quadrants, 100 r to each	42	M	Normal heart	10/28/38, 120/82 11/7/38, 110/62 11/18/38, 124/80 3/13/39, 124/80 6/27/39, 144/98 11/22/40, 132/80	0	0 0 0 0 0 0	0 0 0 0 0 0
11	Hodgkin's disease	A N 1,200 r by 2, mediastinum, anterior and posterior 1,200 r axilla 800 r abdomen 1,200 r left side neck	30	M	Normal heart	4/20/39, 128/84 5/16/39, 124/78	—	+ 0	0 0
12	Lympho sarcoma	O B 1,600 r by 2, mediastinum, anterior and posterior 1,500 r right side neck	30	M	Normal heart	3/31/39, 134/90 5/5/39, 118/80	0	+ 0	0 0
13	Brill Symmer disease (giant follicular lymphoma)	J J 400 r by 6, right and left side neck, right and left axillas and right and left groins	22	M	1 Rheumatic type 2 Cardiac enlargement, mitral in sufficiency, mitral stenosis 3 Regular sinus rhythm 4 Functional capacity I	12/27/38, 112/95 1/23/39, 110/80 3/27/39, 114/76	0	0 0 0	0 0 0
14	Teratoma testis	J N 1,750 r to right side abdomen, anterior 1,750 r to right side abdomen, posterior 3,500 r to epigastrium, anterior 3,500 r to epigastrium, posterior	33	M	Normal heart	6/9/38, 110/60 8/16/38, 130/90	— +	+ +	+ +
15	Teratoma testis	R R 2,000 r by 2, lower abdomen 2,000 r by 2, epigastrium, anterior and posterior 2,000 r by 2, mediastinum, anterior and posterior	28	M	Normal heart	5/2/38, 130/80 6/16/38, 102/76 8/18/38, 130/90	0 0 +	+ + 0	0 0 0
16	Lymphatic leukemia	J C 75 r Huebelen unit	63	M	1 Hypertension, arteriosclerosis 2 Cardiac enlargement, myocardial fibrosis, mitral incompetence, aortic sclerosis 3 Regular sinus rhythm 4 Functional capacity I	10/21/38, 140/82 10/24/38, 148/90	0 0	+ +	+ +
17	Lymphatic leukemia	R II 75 r Huebelen unit	59	F	1 Rheumatic fever (inactive), hypertension, arteriosclerosis 2 Cardiac enlargement, mitral insufficiency, myocardial fibrosis 3 Regular sinus rhythm 4 Functional capacity II	7/16/38, 140/82 7/17/38, 140/82 7/18/38, 160/82 10/31/38, 178/88	0 0 0 —	+ + + +	0 0 0 0
18	Lymphatic leukemia	S K 75 r Huebelen unit	65	M	Normal heart	7/15/38, 120/64 7/17/38, 120/60 7/18/38, 140/60	0 0 0	0 0 0	0 0 0

\* See table 1 for key to table



One patient with marked QRS and T wave changes in the post-treatment electrocardiogram had changes in the position of the heart secondary to a pleural effusion on the left side and infiltration of the lower lobe of the left lung with Hodgkin's disease, which undoubtedly accounted for the alterations in the electrocardiogram

*Group 3*—This group with exception of the patient with tuberculous lymph nodes consists of patients with cancer in the following locations

	Patients
Left breast	15
Right breast	10
Right lung	5
Left lung	6
Esophagus	4
Cardiac end of the stomach	2
Pleura, left side (mesothelioma)	1
Hilus of the left lung (metastatic teratoma)	1
Mediastinum (Hodgkin's disease)	1
Mediastinal lymph nodes (tuberculosis)	1

These patients are placed in the same group because they received fairly heavy radiation to the thorax, and distant parts of the body were not irradiated. There were 17 men and 29 women, ranging in age from 26 to 73 years. Nineteen of the 46 patients had structural heart disease. In 17 patients the heart disease was secondary to hypertension or arteriosclerosis or both, in 1 it was rheumatic in origin and in 1 syphilitic in origin (table 3).

Most patients with carcinoma of the breast received roentgen radiation to the affected breast and axilla through five portals, each portal being given a total of 1,800 r. In some patients this was followed by radical mastectomy. In those patients to whom only a postoperative cycle was given, the axilla alone was given a dose of 1,800 r to each of three portals. Patients with cancer of the lung received radiation through two or three appropriate-sized portals, cross firing the lesion. The total dose for these patients ranged from 2,000 r to 4,200 r per portal. Patients with cancer of the esophagus were treated through two paravertebral and two parasternal portals. Each portal was given from 1,600 to 3,000 r. The remaining 6 patients (those with teratoma, Hodgkin's disease, tuberculosis, etc.) had types of treatment too varied to permit detailed explanation.

In 15 patients the beam of radiation was directed through the bulk of the heart. In 2 patients the lower half of the heart was irradiated. The doses that these hearts received have been accurately estimated. They ranged from 750 r to 5,200 r. The majority of the doses of high voltage radiation were of the order of 1,500 to 2,500 r.

In an undetermined number of the remaining 29 patients (26 with cancer of the breast, 3 with cancer of the lung) only a portion of the heart was irradiated. This needs some further explanation. The radiotherapist in treating cancer of the breast attempts to encompass the lesion and at the same time direct the beam tangentially to the wall of the chest to spare the lung. This was impossible in certain instances because of the location of the lesion or the type of breast with which he had to deal. In these instances the dose that the heart received cannot be estimated.

There were wide variations in blood pressure in the patients of group 3. In 24 it was essentially unchanged during the active phase of radiation therapy, in 16 it fell, and in 6 it was higher at the end of the therapy than before treatment was started (fig 1). Of the 6 patients whose blood pressure rose, 3 had gastrostomy for marked esophageal obstruction before treatment and their nutrition improved markedly during the time that they received roentgen radiation. This again suggests that the maintenance of nutrition is a factor in affecting the blood pressure during radiation therapy just as it was in the patients who had cancer of the head and neck whose blood pressure fell because of insufficient nourishment.

In the entire group there was no evident correlation between alteration of the blood pressure and heart disease, hypertension, anemia, toxemia, infection or the amount of radiation given.

A comparison of the serial electrocardiograms of these patients taken before, during and after roentgen therapy is most interesting. As in groups 1 and 2 there were no significant or permanent changes in the P wave voltages, and the PR and QRS intervals remained constant except in a single instance (see the section entitled arrhythmias, paragraph 4).

The QRS voltage varied widely, frequently and inconsistently. The Q waves were the least affected. The R and S waves were altered as much as 50 per cent from one tracing to its successor. It did not appear to matter whether the right side or the left side of the thorax or the heart itself was irradiated. As a result of these QRS changes, the axis deviation was without its usual import, since the shift was frequently opposite to or greater than the expected one.

On the other hand the changes in  $T_1$  and  $T_3$  were predictable in about 80 per cent of the cases. In those patients who had the area of a cancer of the left breast irradiated either before or after operation, there was a progressive lowering of  $T_1$ , even to a negative phase, followed by a gradual rise toward the pretreatment level. Coincident with the decrease of  $T_1$  there was a rise in the voltage in  $T_3$  followed by a gradual decrease toward its former level.  $T_2$  was raised in some tracings and lowered in others and relatively unchanged in still others (figs 2 and 3).

Conversely, in the patients who had roentgen treatment for carcinoma of the right breast there was a general rise in  $T_1$  followed later by a decrease toward its former level. As  $T_1$  rose,  $T_3$  fell, and then gradually returned to its former level.  $T_2$  rose, fell or remained unchanged (fig 4). However, these changes were of smaller magnitude than those in the patients who had the left side of the thorax treated.

In those patients in whom the center of the thorax was treated—for instance patients with carcinoma of the esophagus, carcinoma of the lung close to the hilum area or mediastinal tumors—there were reciprocal changes in  $T_1$  and  $T_3$ , but they did not conform to the pattern shown by the patients with cancer of the breast and cancer of the lung away from the hilum (fig 5).

Three patients have been observed 2 of whom had pericarditis and the third of whom probably has pericarditis following roentgen treatment. In the first, a woman with cancer of the left lung who was treated heavily twelve years ago, radionecrosis of the ribs developed with secondary empyema and a most severe form of pleuropulmonitis. During the last two years of her life progressive right-sided heart failure developed with all its classic signs, and she died as a result of it. At autopsy chronic pericarditis, partly adhesive in type, and the changes typical of chronic cor pulmonale were encountered. The latter state was induced by compression and torsion of the pulmonary artery due to advanced chronic fibrosing mediastinitis.

TABLE 3 A—Data on Patients in Group 3 Right Breast and Lung \*

Diagnosis	Name and Treatment	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Comment
1 Cancer of right breast	L P August 1938 breast, medial and lateral, supraclavicular space, anterior and poste- rior axilla—2,100 r by 5, 200 kv, at 50 cm S.T.D. Oct 18, 1938 mastectomy	30	F	Normal heart	8/1/38 114/78 8/20/38, 104/72 3/14/39, 114/80	Cough and dyspnea due to radiation fibrosis of right lung
2 Cancer of right breast	A W May 1938 breast, medial and lateral, 1,200 r by 2 June 16, 1938 mastectomy September 1938 right supraclavicular space, anterior and posterior axilla—1,200 r by 3 November 1938 chest, anterior and lateral, 2,400 r by 2	65	F	1 Arteriosclerosis 2 Myocardial fibrosis 3 Regular sinus rhythm 4 Functional capacity I	5/17/38 140/80 9/30/38 146/90 10/28/38 142/00 11/21/38, 128/60 2/7/39, 160/84 6/5/39, 170/98	Cough and dyspnea persistent due to fibrosis of right lung
3 Cancer of right breast	M S March 1939 right supraclavicular space, anterior and posterior, axilla direct—1,800 r by 3 July 6, 1939 mastectomy	36	F	Normal heart	3/27/39 122/80 4/29/40, 130/100	
4 Cancer of right breast	M M April 1939 breast, medial, lateral and in- terior, supraclavicular space, anterior and posterior, axilla—2,100 r by 6 Aug 26, 1939 mastectomy	32	F	1 Hypertension 2 Cardiac enlargement, myo- cardial fibrosis, mitral in- competence 3 Regular sinus rhythm 4 Functional capacity I	4/5/39 170/90 12/14/39 150/90 1/11/40 154/90	Dyspnea due to radiation fibrosis of right lung
5 Cancer of right breast	Y B March 1939 breast, medial and lateral, supraclavicular space, anterior and poste- rior, axilla—2,100 r by 5 August 1939 mastectomy	44	F	Normal heart	3/14/39, 130/90 4/20/39 130/82 8/28/39 134/90 10/9/39, 138/88 1/12/40 132/90 4/11/40 130/90	
6 Cancer of right breast	A M May 1938 breast, medial and lateral, supra- clavicular space, anterior and posterior, axilla—2,100 r by 5	72	F	Normal heart	5/26/38 150/98 6/20/38, 120/90	
7 Cancer of right breast	H K June 1939 supraclavicular space, anterior and posterior, axilla—1,800 r by 3	64	F	1 Hypertension arterio-sclerosis 2 Cardiac enlargement, mitral incompetence, aortic sclerosis 3 Regular sinus rhythm 4 Functional capacity I (or II)	5/2/40, 190/100 5/29/39 162/90 12/28/39, 164/80 1/10/40 160/90 10/21/40, 160/86	Chronic pleuritis at apex of right lung, following radiation therapy

8	Cancer of right breast	R H O March and April 1939 breast, medial and lateral, supraclavicular space, anterior and posterior, axilla-1,800 r by 5	59	F	1 Hypertension, arteriosclerosis 2 Cardiac enlargement, myocardial fibrosis, mitral incompetence, aortic sclerosis 3 Regular sinus rhythm 4 Functional capacity II	3/14/39, 240/120 5/16/39, 210/120 7/16/39, 190/100 11/13/39, 200/110 2/26/40, 210/120	Unchanged, headache and vertigo due to hypertension
9	Cancer of right breast	F C June July 1938 breast, medial, lateral and inferior, supraclavicular space, anterior and posterior, axilla-2,100 r by 6	63	F	1 Hypertension, arteriosclerosis 2 Cardiac enlargement, aortic sclerosis 3 Regular sinus rhythm 4 Functional capacity I (or II)	6/16/38, 160/104 7/14/38, 148/ 88	
10	Cancer of right breast	L V J Breast, medial and lateral, axilla, supraclavicular space, anterior and posterior-2,400 r by 5	49	F	1 Hypertension, arteriosclerosis 2 Myocardial fibrosis, aortic sclerosis 3 Regular sinus rhythm with anginal syndrome 4 Functional capacity I	5/ 4/39 180/110 5/25/39, 160/ 90	
11	Cancer of right lung	L M June 1938 chest, anterior and posterior, 1,950 r by 2 October 1938 chest, anterior and posterior, 1,350 r by 2 November 1938 chest, anterior and posterior, 3,000 r by 2	58	M	Normal heart	4/21/38, 140/ 88 5/ 3/38, 158/ 90 7/28/38 164/ 90 10/11/38, 132/ 90 11/ 1/38, 120/ 86 12/14/38, 150/ 90	Cough and dyspnea persistent during period of observation
12	Cancer of right lung	M B January 1939 chest, anterior and posterior, 3,800 r by 2 July 1939 chest, anterior and posterior, 2,400 r by 2	52	M	Normal heart	12/30/39, 118/ 76 2/ 2/40, 160/ 90 3/17/40, 142/ 80 4/8/40, 148/ 80 8/22/40, 130/ 80	
13	Cancer of right lung	A P April 1938 right supraclavicular space, 1,500 r, right axilla, 1,000 r	63	M	Arteriosclerosis, normal heart	4/26/38, 120/ 82 5/15/38, 112/ 78	
14	Cancer of right lung	H G January 1939 chest, anterior and posterior, 4,000 r by 2 June 1939 mediastinum, anterior and posterior, 1,000 r by 2	60	M	Normal heart	1/29/39, 140/ 80 3/17/39, 140/ 90 5/ 2/39, 138/ 80	

\* See table 1 for key to table

TABLE 3B—Data on Patients in Group 3 Left Breast and Lung \*

Diagnosis	Name and Treatment	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Comment
1 Cancer of left breast	L M July 1938 supraclavicular space, anterior and posterior 10 by 13 cm., axilla—1,800 r by 3 May 27, 1938 mastectomy	36	F	Normal heart	5/13/38, 110/ 72 7/17/38, 124/ 82	
2 Cancer of left breast	R W July 6, 1938 radical mastectomy Aug 15, 1938 supraclavicular space anterior and posterior axilla direct—1,800 r by 3	37	F	1 Rheumatic fever (inactive) 2 Cardiac enlargement, mitral insufficiency, mitral stenosis 3 Regular sinus rhythm 4 Functional capacity I	6/10/38 106/ 80 7/21/38 102/ 80 9/23/38, 112/ 78 1/ 3/39 100/ 64 6/19/39, 112/ 90	Signs of pulmonary fibrosis roentgen evidence of fibrosis of left lung
3 Cancer of left breast	M I April May 1938 breast, medial and lateral, 1,800 r each breast, 4 portals, 600 r each supraclavicular space, anterior and pos terior, 1,800 r each, axilla 1,800 r	51	I	1 Syphilis 2 Cardiac enlargement, aortic insufficiency 3 Regular sinus rhythm 4 Functional capacity I	4/11/38, 160/ 40 5/12/36 200/ 80 8/18/38 182/ 60 11/21/38, 200/ 60 2/11/39 170/ 58	Signs of pulmonary fibrosis roentgen evidence of fibrosis of left lung
4 Cancer of left breast	A \ October 1938 breast direct and lateral, 1,800 r each, supraclavicular space, anterior and posterior, 1,800 r each, axilla 1,800 r	67	I	1 Hypertension arterio-sclerosis 2 Cardiac enlargement, mitral incompetence 3 Regular sinus rhythm 4 Functional capacity I	10/11/38 210/110 10/21/38 210/110 11/ 3/38, 200/106 2/ 7/39, 180/ 90	Symptoms of acute radiation pneu monitis
5 Cancer of left breast	L I March 1939 breast, lateral and medial, 2,000 r each, breast, inferior, 2,400 r, supra clavicular space, anterior and posterior, 2,000 r each, axilla, 2,000 r	63	F	1 Hypertension 2 Cardiac enlargement 3 Regular sinus rhythm 4 Functional capacity I	3/ 9/39 200/100 1/ 6/39 210/100	Symptoms of acute radiation pneu monitis
6 Cancer of left breast	R O June 1938 breast, lateral, medial and in ferior, 2,250 r each axilla, anterior pos terior and direct, 1,800 r each, Aug 12, 1938 mastectomy	64	I	1 Arterio-sclerosis 2 Myocardial fibrosis 3 Regular sinus rhythm 4 Functional capacity I	5/26/38, 150/ 80 7/11/38, 108/ 68 11/28/38, 118/ 92 1/27/39, 126/ 82 4/27/39 134/ 80 5/ 8/39, 130/ 82	Signs of pulmonary fibrosis in left lung
7 Cancer of left breast	C C June and July 1938 breast, medial and lateral, 2,100 r each axilla, anterior, pos terior and direct	47	F	Normal heart	6/24/38, 140/ 85 8/ 8/38, 138/ 90 9/26/38 121/ 88 12/12/38, 130/ 80 1/11/39 152/ 90 6/ 7/39	Signs of chronic radiation fibrosis in left lung

8	Cancer of left breast	I L May 1939 breast, lateral, medial and inferior, 2,400 r each, supraclavicular space, anterior and posterior, axilla—2,100 r each July 15, 1939 mastectomy	43	F	1 Essential hypertension 2 Normal heart	1/26/39, 150/100 5/17/39 130/100 8/17/39 12/ 7/39, 142/ 90 4/26/40 7/ 2/40, 146/ 96 10/10/40, 140/100	Roentgen evidence of pulmonary fibrosis in left lung
9	Cancer of left breast	A D May 1938 breast, anterior and lateral, supraclavicular space, anterior and posterior, axilla—2,100 r each October 1938 radical mastectomy	50	F	Normal heart	5/17/38, 132/ 80 6/27/38, 112/ 70 9/24/38 104/ 70	
10	Cancer of left breast	G S July 1938 mastectomy November 1938 left axilla and left supraclavicular space, 1,800 r each anterior wall of chest, low voltage, 1,200 r	61	F	1 Hypertension, arteriosclerosis 2 Myocardial fibrosis, cardiac enlargement 3 Left bundle branch block 4 Functional capacity I	7/26/38 132/ 90 11/17/38, 142/ 84 12/15/38, 148/ 80 2/ 2/39, 110/110 5/ 9/39, 150/100 7/14/39 10/24/39 1/26/40 150/ 90 4/16/40 134/ 80	1 vertion and palpitation unchanged throughout period of observation
11	Cancer of left breast	V L April and May 1939 breast, lateral, medial and direct, axilla, supraclavicular space, anterior and posterior—2,100 r each February 1940 left breast, medial, lateral and inferior, 900 r each	69	F	1 Rheumatic fever, arteriosclerosis 2 Cardiac enlargement, mitral insufficiency 3 Regular sinus rhythm with premature ventricular contractions 4 Functional capacity I	5/14/39, 148/ 80 1/13/39, 160/ 80 6/ 7/39 7/ 3/39 10/23/39 2/ 5/40 4/28/40 10/10/40, 140/ 80	Roentgen evidence of pulmonary fibrosis in left lung
12	Cancer of left breast	G K May June 1938, breast, direct, and supraclavicular space, 2,000 r each, axilla, 1,500 r	28	F	Normal heart	1/18/38, 134/ 68 9/ 6/38	
13	Cancer of left breast	T W April 1939 supraclavicular space, anterior, posterior and axilla, 1,800 r each (high voltage)	36	F	Normal heart	3/23/39 118/ 80 5/ 9/39, 108/ 72	
14	Cancer of left breast	T B June and July 1938 breast, direct, 2,400 r, axilla, anterior, posterior and direct, 2,100 r each, left wall of chest, lateral, 3,100 r	65	F	1 Hypertension, arteriosclerosis 2 Cardiac enlargement, myocardial fibrosis, mitral incompetence 3 Auricular fibrillation 4 Functional capacity II	6/ 2/38, 132/ 80 7/11/38, 112/ 70 8/ 8/38, 104/ 70	Palpitation and dyspnea unchanged
15	Cancer of left breast	T W December 1939 axilla, direct, and supraclavicular space, 1,800 r each anterior wall of chest, 1,500 r (low voltage)	44	F	Normal heart	12/ 6/39, 140/ 80 1/ 3/40, 144/ 80 4/ 2/40, 140/ 80 6/26/40, 118/ 70 10/26/40, 138/ 94	

\* See table 1 for key to table

TABLE 3C—Data on Patients in Group 3 Mediastinum \*

Diagnosis	Name and Treatment	Age	Sex	Cardiovascular Diagnosis	Blood Pressure	Dose Delivered to Heart	Comment
1 Mesothelioma of pleura, left side	S K April 1938 mediastinum, anterior and posterior, 600 r each December 1938 mediastinum, anterior and posterior, 1,200 r each, 10 cm cone at 70 cm	42	F	Normal heart	4/ 4/38, 138/80 4/25/38 12/ 2/38, 118/80 12/20/38, 140/82 1/13/39, 140/82	900 r	Persistent cough and dyspnea
2 Tuberculosis of hilar nodes	J H April June 1938 mediastinum, anterior, 1,000 r, mediastinum, posterior, 1,100 r, portal 11 x 14 cm	27	F	Normal heart	5/ 6/38, 112/84 5/25/38, 106/78 1/19/39, 128/82	750 r	Pregnant 7 months
3 Cancer of esophagus	F P Two parasternal and two paravertebral portals, 14 x 17 cm, 1,600 r each, at 70 cm	51	F	Normal heart	11/ 1/38, 160/80 11/26/38, 110/90	2,000 r	Marked cachexia and anemia
4 Hodgkin's disease	I K June through August 1938 mediastinum, 1,800 r by 4, each portal 4 x 6 cm, right and left side of neck, 2,400 r each left axilla, 2,400 r January 1939 epigastrium, anterior, 600 r, portal 10 x 10 cm, February 1940 spleen, anterior, 600 r, portal 8 x 10	26	F	Normal heart	6/14/38, 128/80 9/27/38, 114/80 4/20/39, 131/90 10/ 2/40, 130/80	1,000 r	
5 Cancer of esophagus	F F 2,500 r by 4 (2 parasternal and 2 paravertebral portals), 1,000 kv machine, 14 x 7 cm portals at 70 cm	67	M	1 Arteriosclerosis 2 Cardiac enlargement, mitral incompetence 3 Regular sinus rhythm 4 Functional capacity I	12/15/39, 148/80 12/28/39, 130/100 1/25/40, 118/80 2/ 3/40, 128/86 3/14/40, 128/90 4/11/40, 130/100 5/23/40, 150/100 10/ 3/40, 130/90	4,000 r	Bilateral hilar radiation pneumonitis
6 Cancer of esophagus	T M 3,000 r by 4 (through 2 parasternal and 2 paravertebral portals), 1,000 kv machine, 14 x 7 cm at 70 cm	71	M	1 Arteriosclerosis 2 Cardiac enlargement, mitral incompetence, myocardial fibrosis 3 Left heart block 4 Functional capacity II	5/ 9/40, 134/80 6/23/40, 130/90 7/10/40, 110/60 8/ 5/40, 130/90 10/ 3/40, 130/80	5,200 r	Cachectic, bronchopneumonia, mediastinitis
7 Cancer of esophagus	O G 1,250 r through each of 4 portals, 14 x 7 cm, at 70 cm	57	M	Normal heart	11/17/39, 100/74 11/28/39, 116/70	2,150 r	Died mediastinitis
8 Cancer of cardiac end of stomach and esophagus	Dr T 2,500 r through each of 4 portals, 2 anterior and 2 posterior, 200 kv at 60 cm	53	M	Normal heart	10/ 6/38, 80/62 12/15/38, 96/68	3,100 r	Mediastinitis

9	Cancer of cardiac end of stomach	G O Epigastrium, anterior and lateral, 12 x 12 cm, 2,250 r each, epigastrium, posterior, 2,100 r, 200 kv at 60 cm	56	M	Normal heart	7/18/38, 120/ 80 8/18/38, 112/ 20 10/ 6/38, 132/ 90	1,600 r	
10	Cancer of hilus of right lung	I C May 1939 mediastinum, anterior and posterior, 2,200 r each, 10 cm cone at 60 cm	73	M	1 Hypertension, arteriosclerosis 2 Myocardial fibrosis, cardiac enlargement 3 Auricular fibrillation 4 Functional capacity I	4/ 4/39, 160/ 98 4/21/39, 160/110 6/29/39, 170/110	1,350 r	Recovered, auricular fibrillation
11	Metastatic teratoma of hilus of left lung	H R Mediastinum, anterior and posterior, 80,000 mg hr each	39	M	1 Arteriosclerosis 2 Coronary sclerosis 3 Regular sinus rhythm, anginal syndrome 4 Functional capacity II	9/28/35, 138/ 98 12/30/37, 130/ 90 9/30/38, 132/ 90	1,200 r	Died acute coronary occlusion
12	Cancer of hilus of left lung	C C December 1938 mediastinum, anterior and posterior, 10 cm 3,000 r each August 1939 mediastinum, anterior and posterior 8 cm, 1,500 r each, 200 kv at 70 cm	57	M	Normal heart	12/ 1/38, 142/ 80 12/20/38, 112/ 70 1/13/39, 98/ 70 3/23/39, 120/ 80 7/11/39, 134/ 90 11/30/39, 130/ 90	2,100 r	Mediastinal pleuritis
13	Cancer of hilus of left lung	W R Mediastinum, anterior and posterior, 3,000 r each, lateral wall of chest, 2,400 r, portals 14 x 9 cm, 200 kv at 70 cm	53	M	Normal heart	12/ 1/38, 116/ 78 1/ 5/39, 108/ 80	2,000 r	
14	Cancer of lower lobe of left lung	B L June 1938 mediastinum, anterior and posterior, 3,000 r each, 200 kv at 70 cm	57	M	1 Hypertension, arteriosclerosis 2 Myocardial fibrosis 3 Regular sinus rhythm 4 Functional capacity I	5/26/38, 180/130 8/18/38, 142/ 98	1,500 r	Paralysis agtans
15	Cancer of lower lobe of left lung	H P April and May 1938 mediastinum, anterior and posterior, 2,250 r each, portals 10 x 6 cm, 200 kv at 50 cm	62	M	Normal heart	4/11/38, 138/ 72 5/18/38 10/ 4/38, 140/ 92 2/17/39, 130/ 90 8/ 2/39, 120/ 80	1 100 r	Two attacks paroxysmal auricular tachycardia, later paroxysmal auricular fibrillation
16	Cancer of lower lobe of left lung	A S Mediastinum, anterior and posterior, 3,000 r each, 1,000 kv machine, 13 cm cone	54	M	Normal heart	10/10/39, 120/ 90 10/16/39, 100/ 60 10/24/39, 92/ 68 10/31/39, 92/ 64 11/17/39, 90/ 68	2,450 r	
17	Cancer of lower lobe of left lung	J K Mediastinum, anterior and posterior, 3,000 r each, at 70 cm, 200 kv, 10 cm cone	62	M	Normal heart	4/12/38, 160/ 80 5/17/38, 130/ 80	2 100 r	

\* See table 1 for key to table



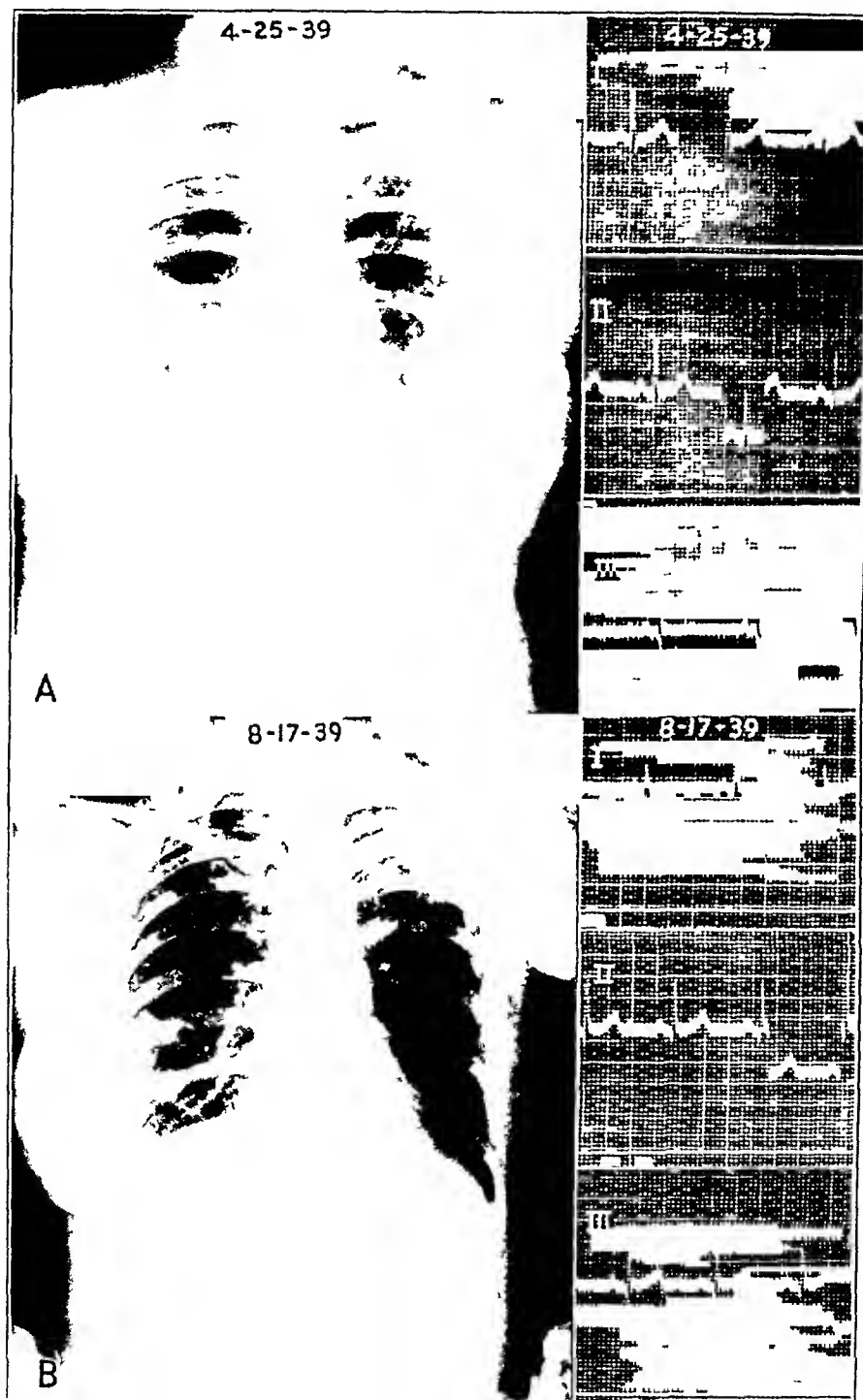
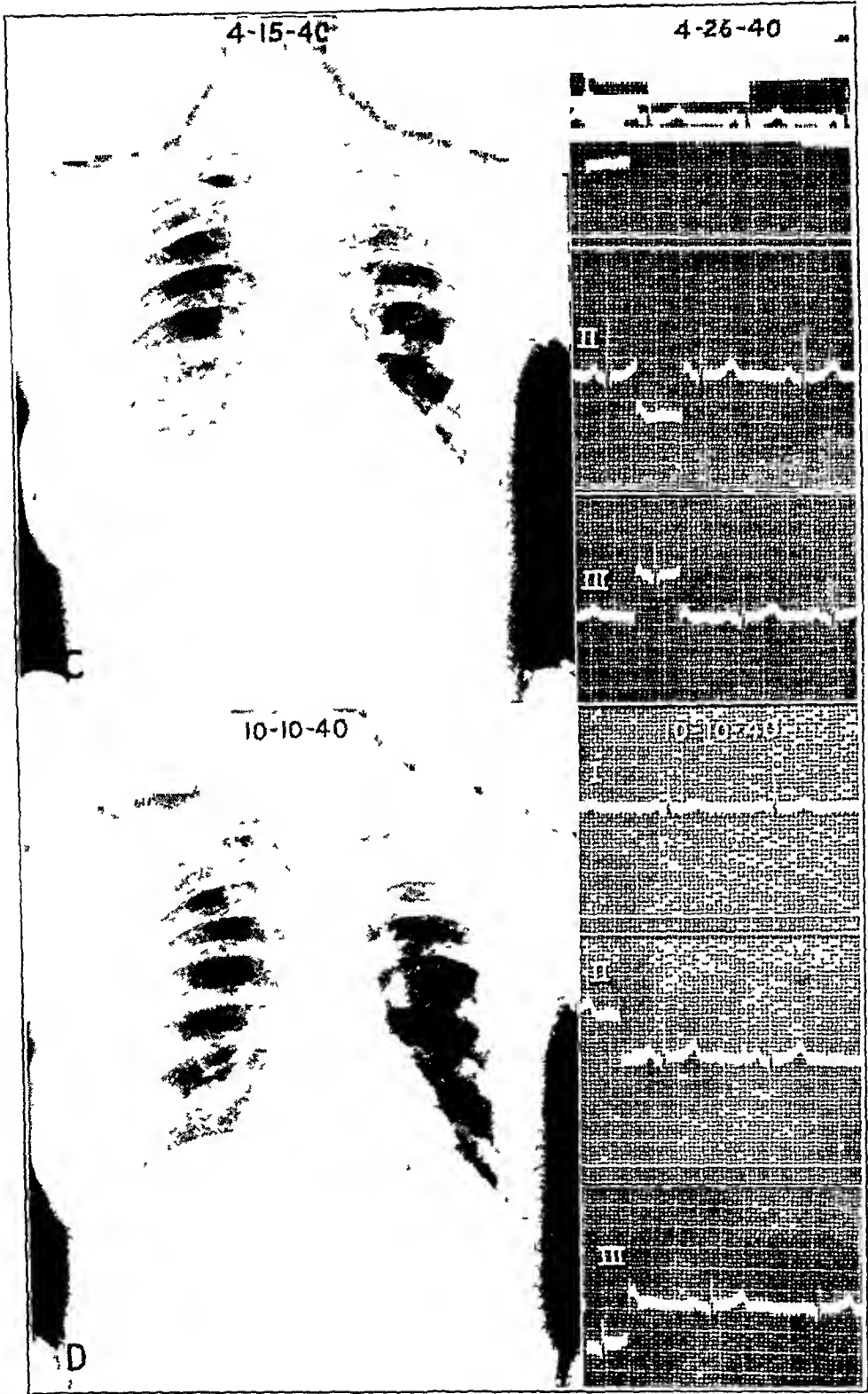


Fig 2—*A* Before treatment. A roentgenogram of the chest and an electrocardiogram of L L, a woman aged 43 with cancer of the left breast.

*B* After roentgen therapy and radical mastectomy. Note the radiation pleuropulmonitis in the upper part of the left lung. T<sub>1</sub> is almost isoelectric, and T<sub>2</sub> has increased voltage.



C Twelve months after roentgen therapy The radiation pleuropulmonitis persists but has decreased  $T_1$  has increased and  $T_3$  has decreased voltage

D Eighteen months after treatment The radiation fibrosis persists This patient had no cardiac or pulmonary symptoms at any time

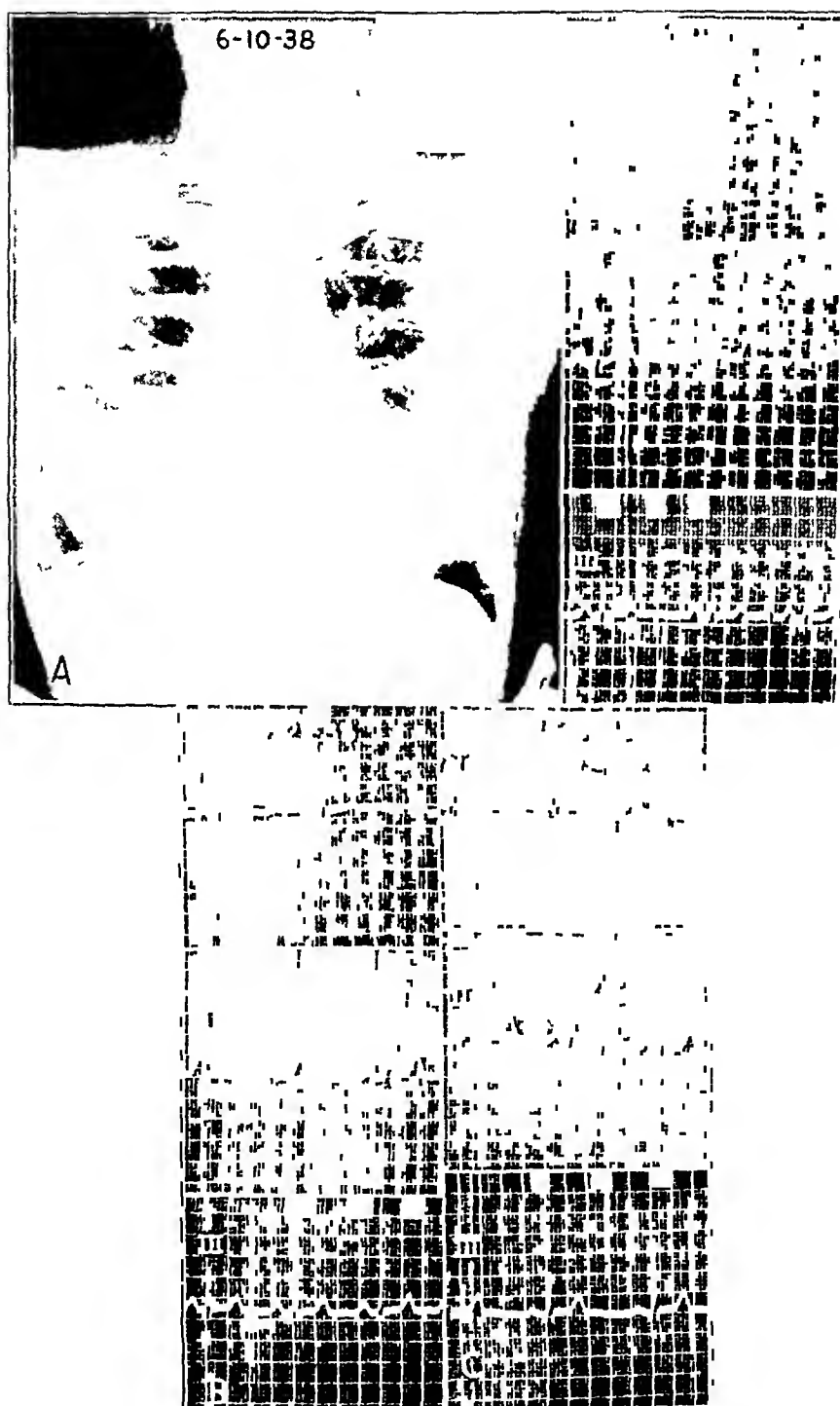
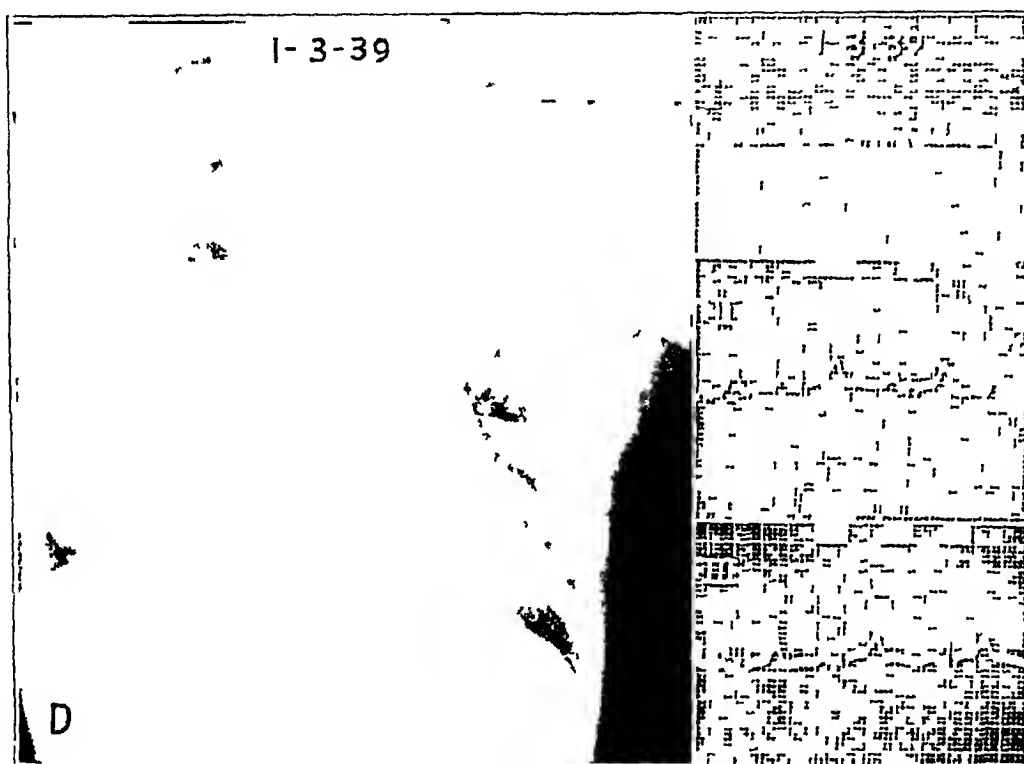


Fig 3—*A* Before treatment A roentgenogram of the chest and an electrocardiogram of R W, a woman aged 37 with cancer of the left breast and rheumatic heart disease  
*B* After mastectomy Note the marked decrease of  $T_1$  and the increase of  $T_2$ . There were no cardiac or pulmonary complications before or after operation  
*C* Immediately after roentgen therapy

The second patient at the time of writing is a woman aged 45 who was treated for cancer of the left breast six years ago. A severe form of radiation fibrosis of the lung and radionecrosis of the anterior portion of the ribs and overlying skin on the left side developed, which is progressing. Three years ago she began to complain of increasing dyspnea, edema of dependent parts and ascites. At present she has all the classic signs of constricting pericarditis and signs of chronic radiation pleuropulmonitis of the lower lobe of the left lung. The venous pressure is markedly elevated. A biopsy of her liver done two years ago showed "cardiac cirrhosis." A kymogram shows markedly decreased pulsations of both the left and the right side of the heart.

The third patient is a woman aged 35 who also received heavy irradiation of the left side of the chest for cancer of the breast and in whom a severe degree of pulmonary fibrosis developed. Necrosis of the soft tissue of the anterior aspect of the thorax on the left side and of the subjacent ribs developed, and a low grade infec-



D Seven months after roentgen therapy, four months after operation. T<sub>1</sub> is almost isoelectric. Note the radiation fibrosis in the upper part of the left lung. The patient complained of some dyspnea and cough.

tion of the left lung occurred later. Her complaints since then have been largely dyspnea, cough, expectoration and occasional hemoptysis. The pulsations of the heart on the left side cannot be detected fluoroscopically, either because they are so small in amplitude or because the left lung is too dense. A kymogram, while not conclusive, is strongly suggestive of pleuropericardial adhesions on the left side. To date she has never experienced cardiac failure. Her electrocardiogram shows isoelectric T waves in all leads. This may be due to myocardial degeneration but is probably due to pericardial adhesions.

All these patients are similar in that they received heavy roentgen radiation and chronic infection of the thoracic wall, ribs and left lung developed. As the infection progressed by contiguity, the pericardium was invaded. One can assume either that the pericarditis was caused primarily by roentgen therapy or that the

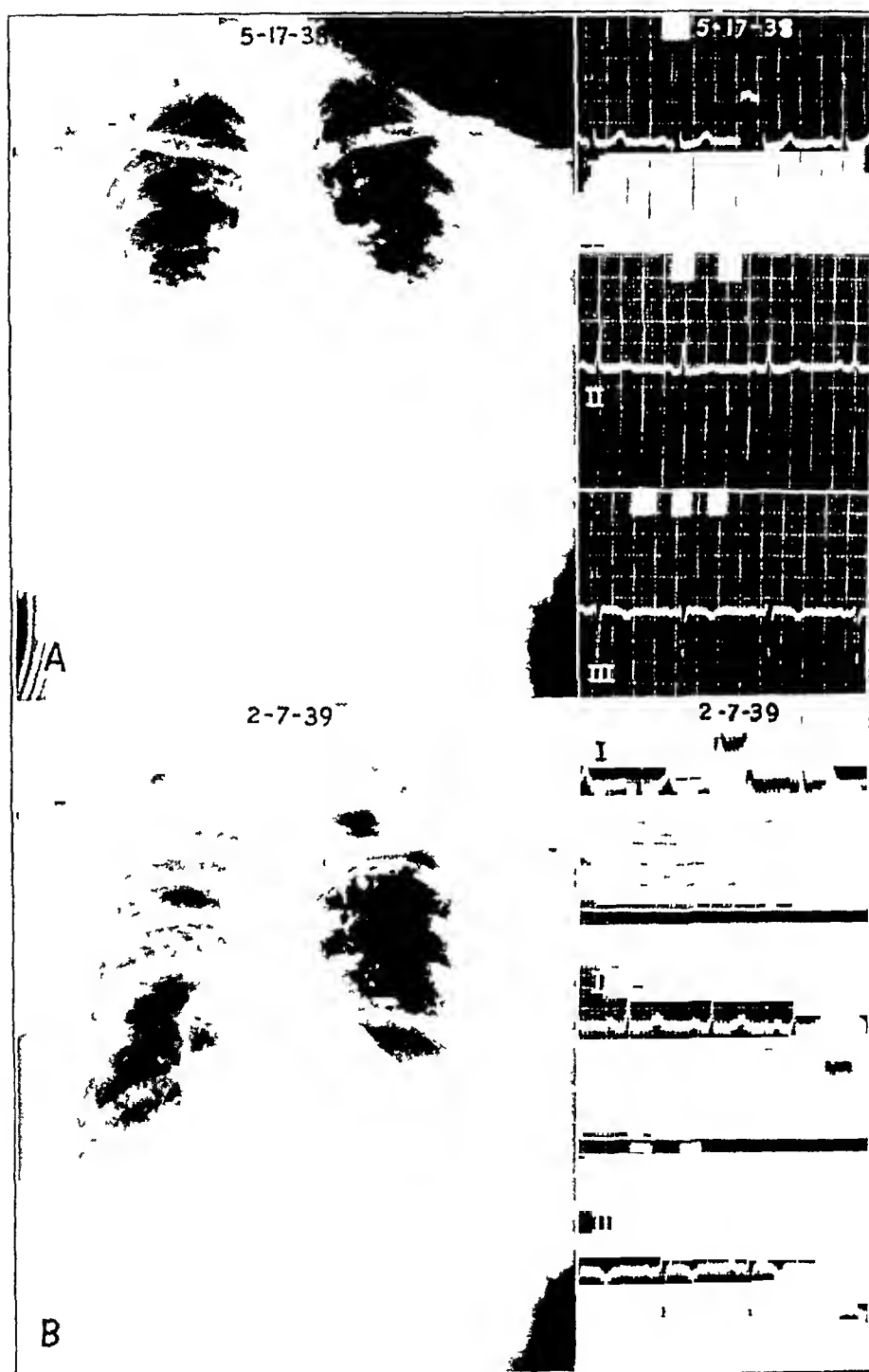
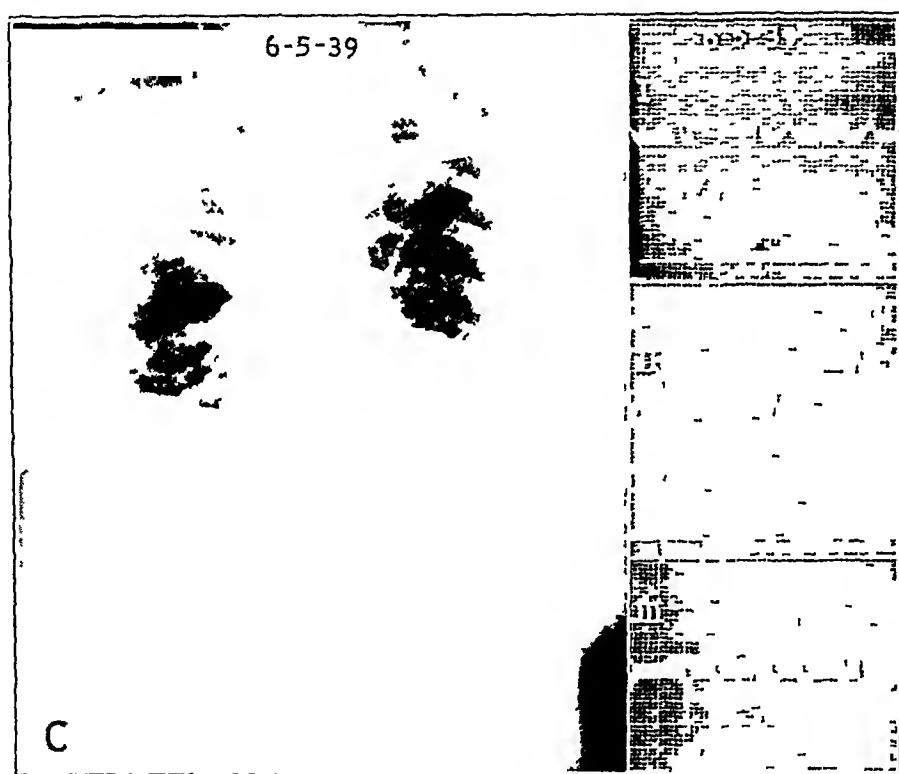


Fig 4—*A* Before treatment. *A* Roentgenogram of the chest and an electrocardiogram of A W, a woman aged 65 with cancer of the right breast.

*B* Eight months after mastectomy and two courses of roentgen treatment. Note the radiation pleuropulmonitis in the upper half of the right lung. In the electrocardiogram  $T_1$  and  $T_2$  have increased and  $T_3$  has decreased voltage.

therapy started a chain of events and the secondary infection was the real cause of the pericarditis. The latter explanation seems more likely.

One patient with teratoma with bulky metastases in the upper left portion of the mediastinum and the left supraclavicular space was treated heavily with radium pack (80,000 milligram hours at 10 cm) in 1936. The upper portion of the heart was included in the beam of radiation. For a few years prior to this he had complained of vague symptoms suggestive of coronary insufficiency with angina of effort. In 1938 he had well marked symptoms of coronary insufficiency. In 1939 he died suddenly in an attack that was reported to be typical of coronary occlusion. At autopsy the heart showed marked fibrosis, but the endocardium and the pericardium were normal. The degree of coronary arteriosclerosis present did not differ in any way from that seen in a patient who had not had radiation therapy. There was nothing on gross or microscopic examination to suggest any peculiar effect of the gamma rays on the heart.



C Twelve months after mastectomy. The roentgenogram was made after a third course of roentgen therapy to the right wall of the chest. The right hemidiaphragm has ascended, and the pleuropulmonitis has increased. The electrocardiogram is unchanged.

*Arrhythmia*—Of the 85 patients studied, 10 had different types of arrhythmia before, during or after treatment. One patient with rheumatic heart disease had premature auricular contractions all during the period of observation. One patient with coronary sclerosis and myocardial fibrosis had premature ventricular contractions all during the follow-up period. The contractions were unchanged in frequency. One patient had premature ventricular contractions after being treated for carcinoma of the cardiac end of the stomach with extension up into the esophagus. This occurred at a time when there was a question of a low grade inferior posterior mediastinitis due to extension of esophageal infection. Whether this was a factor in producing the premature contractions is problematic, since many patients with lower mediastinitis have been observed in the hospital and cardiac arrhythmia has not been unusually frequent.

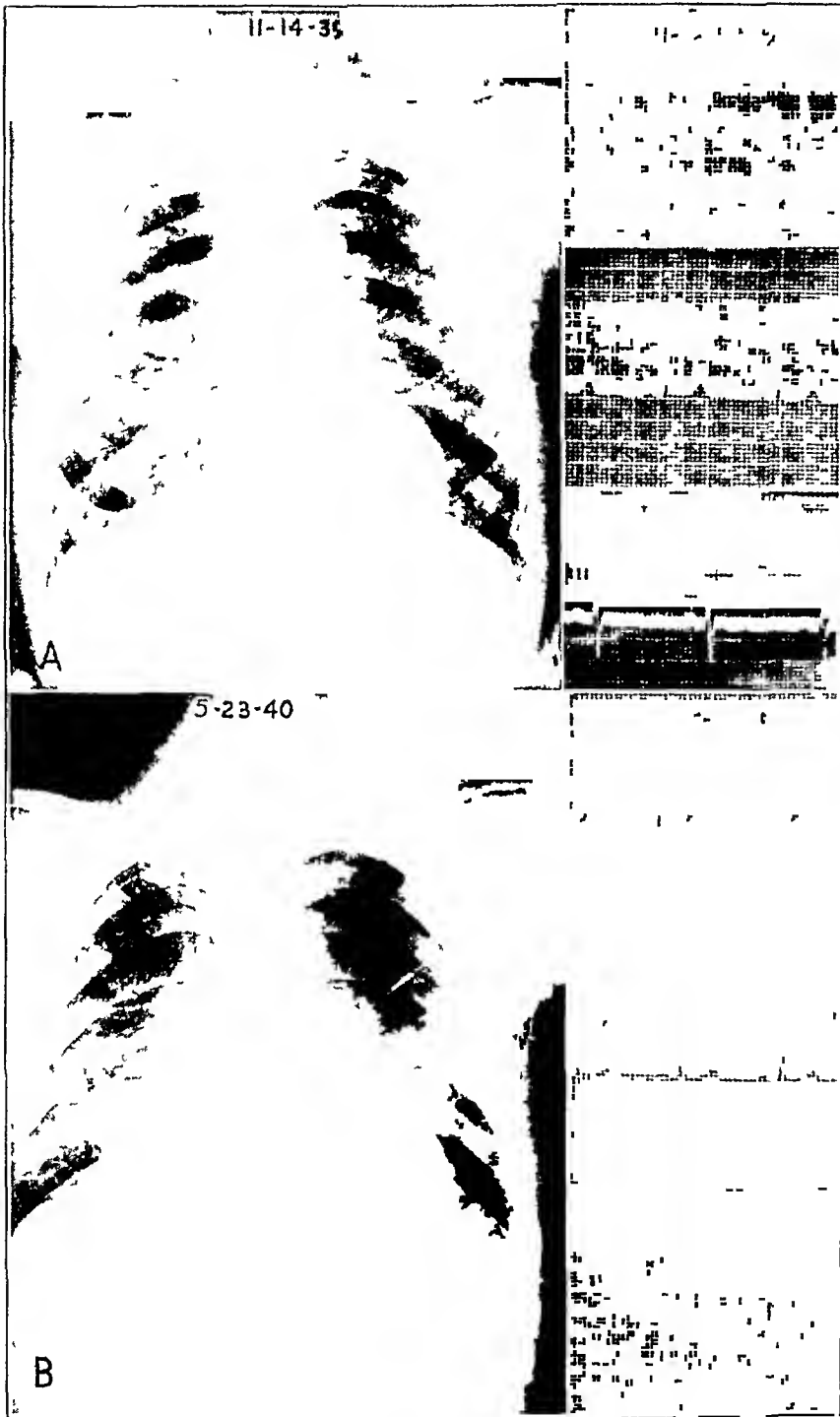
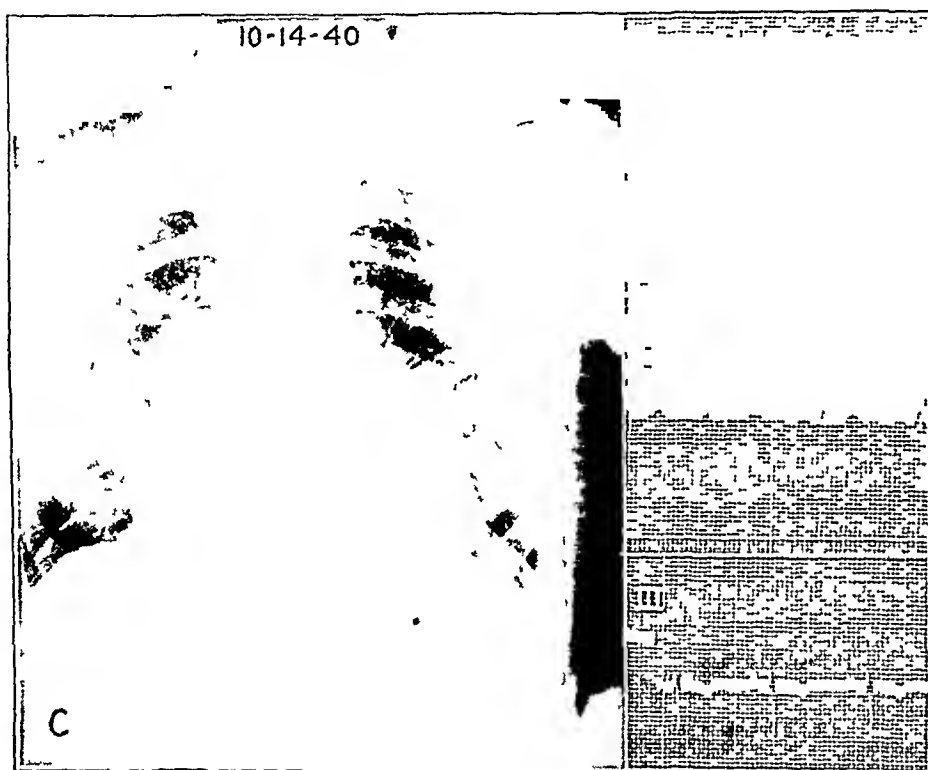


Fig 5—*A* Before treatment A roentgenogram of the chest and an electrocardiogram of E F, a man aged 67 with cancer of the esophagus

*B* After roentgen treatment Intensive roentgen therapy with a 1,000 kilovolt machine had been given Note the marked degree of radiation pleuropulmonitis  $T_1$  has increased and  $T_2$  and  $T_3$  decreased voltage The patient complained of slight dyspnea on exertion and cough

Three patients with heart disease had auricular fibrillation before treatment. The fibrillation persisted during and after therapy and responded to the usual amount of digitalis. Their management was not more difficult than if radiation had not been given.

One patient had two attacks of paroxysmal auricular tachycardia, one during treatment and one many months after treatment. He was treated for both attacks by his local physician with digitalis, and regular sinus rhythm was restored in twenty-four and forty-eight hours, respectively. This same patient had an attack of auricular fibrillation shortly after paralysis of the left vocal cord developed as a result of extension or metastasis of a carcinoma of the left main bronchus to the hilar region with interruption of the recurrent laryngeal nerve. This was again treated by digitalization, and regular rhythm was restored. The paralysis of the left vocal cord persisted until death.



C Eleven months after treatment. Radiation pleuropulmonitis persists.  $T_s$  shows slightly increased voltage. At this time the patient was free of pulmonary symptoms and was gaining weight and strength.

One patient had a left bundle branch block before treatment. This persisted unaltered all during the post-treatment period. One patient had a first degree heart block and received heavy radiation directly through the entire heart by four ports. An electrocardiogram taken one day before death showed a reduction of the PR interval from twenty-four hundredths to two tenths of a second.

#### COMMENT AND SUMMARY

There were two possible ways in which these patients might have been grouped for study. One was to separate those that had heart disease from those with normal hearts and compare the effect of radiation in each group. The other way, as was done here, was to group them on the basis of the region of the body irradiated. From the results that have been obtained it seems that the effect, if any, depends on



the location and treatment of the cancer rather than on the presence or absence of antecedent heart disease

It is undoubtedly true that the changes in the blood pressure during and after treatment depend on (1) depressive effect of the radiation itself, (2) fever, (3) toxemia, (4) infection, (5) anemia and (6) cachexia. A factor that is probably just as important as all of these other agents is nutrition.

In the patients with cancer of the head and neck in whom dysphagia interfered with ingestion of food the fall in blood pressure was striking. As soon as the dysphagia disappeared and proper feeding was established, the blood pressure rose again. Three patients who had esophageal obstruction relieved by gastrostomy before roentgen treatment was instituted had an increased blood pressure during and after the time they received roentgen therapy. Apparently this was also due to increased intake of food.

TABLE 4—*Types of Cardiac Arrhythmia Observed*

Patient	Sex	Before Therapy	After Therapy	Comment
1	F	Premature auricular contraction	Premature auricular contraction	No change
2	M	Auricular fibrillation	Auricular fibrillation	No change, usual response to digitalis
3	F	Auricular fibrillation	Auricular fibrillation	No change, usual response to digitalis
4	M	Auricular fibrillation	Auricular fibrillation	No change, usual response to digitalis
5	M	0	Paroxysmal tachycardia 2 attacks, auricular fibrillation	Both attacks subsided
6	F	Left bundle branch block	Left bundle branch block	No change
7	M	Complete heart block 1st degree	Complete heart block 1st degree	Auriculoventricular conduction time reduced from 0.24 to 0.20 second one day before death
8	M	Premature ventricular contraction	Premature ventricular contraction	No change
9	F	Premature ventricular contraction	Premature ventricular contraction	No change
10	M	0	Premature ventricular contraction	Posterior mediastinitis?

The fall of blood pressure in patients who received roentgen radiation directly through the heart for treatment of pulmonary cancer was not as striking as that in the patients with cancer of the head and neck.

Those patients who had cardiovascular complications have already been discussed in the respective groups. In summary there was no evidence that roentgen therapy per se caused the complications that arose. Those with pericarditis and those with the carotid sinus syndrome had a particular set of conditions arising from both the treatment and the disease itself. In the patients with the carotid sinus syndrome it was probably infection and metastases in the cervical nodes plus treatment. In the patients with pericarditis it was radiation pneumonitis plus secondary infection. In these last patients infection seemed to play the major part in the complications produced.

*Physical Signs and Symptoms*—It was extremely difficult at times to evaluate the symptoms and signs in patients who had radiation to the thorax. This was particularly true in patients who had radical mastectomy, especially if the operation was for cancer of the left breast. There were two distinct reasons for this difficulty.

One concerned the radiation and one the operation. In many patients both factors were present. Certain events frequently take place in the thorax when the structures within are irradiated. At first acute radiation pleuropulmonitis may develop. If severe enough this may progress to the chronic form of the disease with permanent displacement of the heart toward the affected side, decreased mobility of the diaphragm and in many instances partial fixation of the wall of the chest due to fibrosis of the parietes.

This deformation of the lungs, the mediastinum and the wall of the chest gives rise to (1) dyspnea, (2) cough, (3) pleural pain, (4) occasional hemoptysis and (5) reduced vital capacity.

The dyspnea has certain qualities that distinguish it from cardiac dyspnea. It varies with weather conditions, increases only with effort and often changes little quantitatively over a long period. When it is severe, it is almost always accompanied by cough. There is never any edema or increased pressure in the peripheral veins unless there is complicating mediastinal fibrosis, marked mediastinal distortion or heart disease with congestive failure.

The cough is either dry or productive of scant white mucus. It occurs in paroxysms and is usually worse on arising, on retiring and during exercise. Hemoptysis is infrequent, and when it occurs is almost always preceded by severe paroxysms of cough.

As a result of the displacement of the mediastinum and partial immobilization of the diaphragm and wall of the chest, physical signs elicited on examination are sometimes unusual. The heart may appear to be enlarged to the left. The apical impulse is unusually forceful and may simulate a systolic thrill. Murmurs when present before may be exaggerated or otherwise altered. The pulmonic second sound is often relatively accentuated.

The symptoms and signs may cause the physician to wonder if he is dealing with an induced form of heart disease. With the exception of the 3 patients with pericarditis, whose cases are special instances, there has been no clinical evidence of organic cardiac disorder consequent to radiation therapy. This observation is supported by additional clinical data obtained from the study of over 75 patients with long-standing radiation fibrosis of the lung. In none of these has there been evidence of heart disease provoked by the roentgen therapy.

The vital capacity of the patients who had radiation to the thorax was almost always reduced. This was because of (1) pneumonitis, (2) mediastinal displacement, (3) impaired motion of the diaphragm and (4) immobility of a portion of the thoracic wall. The reduction was temporary if the pneumonitis was mild, recovery complete and the other factors nonoperative. If the pneumonitis became chronic, mediastinal displacement permanent and fixation of the parietes persistent, the vital capacity remained lowered.

Contrary to Gendreau's observations, cardiac arrhythmia occurring as a result of roentgen treatment has been infrequent in these patients. One patient in whom premature ventricular contractions developed apparently had a low grade posterior inferior mediastinitis. This may have been a cause for the ectopic beats. The other patient, who had two attacks of paroxysmal auricular tachycardia, was interesting in that the first occurred during treatment and the second many months after treatment was stopped. The tachycardia may have been due to the therapy itself, but it may also have been due to hilar metastasis, since shortly after the second attack he had attacks of paroxysmal auricular fibrillation, and coincidentally with this palsy referable to involvement of the left recurrent nerve developed. From the roentgenograms it was impossible to tell how extensive the disease in the

hilar region was. One can only surmise that involvement of the left vagus nerve or even invasion of the auricular myocardium by neoplastic disease may have been the cause of the fibrillation.

*Electrocardiographic Changes*—There has been a large number of papers reporting the changes in the electrocardiograms as a result of altering either the position of the leads in relation to the heart or the relation of the heart to the thoracic cavity. Notable among these have been the observations published by Einthoven,<sup>11</sup> Katz and associates,<sup>12</sup> Kountz and co-workers,<sup>13</sup> Meek and Wilson<sup>14</sup> and many others.<sup>15</sup> In these reports, however, the emphasis has been placed on the variations of the QRS complexes as the position of the heart was changed or as one or more of the cardiac chambers increased in size. Some mention has been made of changes in the configuration of the T waves, but no special reference or explanation relative to them was made.

From a study of the serial electrocardiograms of these patients two general types of variations can be seen. One is the minor variation of all the waves, more marked in some than in others, that occurred in all of the patients. Since this type was present in patients both with and without heart disease, the only logical explanation is that it represented the reaction of the myocardium to infection, toxemia, altered nutrition, general effect of the roentgen rays, anemia or the neoplastic disease itself. In some patients only a few of these factors were important, in others all might have played a part.

The other type of variation was that seen in the patients who had radiation directed to the thorax. While there were some variations in P, Q, R and S waves in the electrocardiograms, they were extremely wide and unpredictable. The T wave changes were consistent, and in many instances one could forecast the alteration that took place. These changes were present in patients with and without heart disease and were most marked when the patient received radiation for cancer of the breast and when there was appreciable evidence both on physical examination and in roentgenograms that radiation fibrosis of the lung with some mediastinal displacement was present. They were less striking when the heart itself was irradiated (see figures 2 through 5).

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It is probable that another cause for the T wave changes is the fixation of the thoracic wall. Evidence supporting this is the fact that similar changes have been observed in the electrocardiograms of patients after radical mastectomy, before radiation therapy was started (fig 3). There was such a patient in this series, and since this patient was seen, others have been observed. The changes are likely to be more marked when mastectomy has been done on the left side. One possible explanation is that there may be an appreciable degree of compensatory emphysema of the contralateral lung when the homolateral lung is partially fixed or compressed by a partially rigid thoracic wall. With these changes there would be a relative shift of the mediastinum toward the affected side.

It seems quite certain that the electrocardiographic changes observed cannot be caused by heart disease. They are present to a lesser degree in the great majority of the patients operated on for cancer of the breast as a result of the mastectomy alone. These changes are not supported by symptoms and signs of heart disease.

Unfortunately, there are not adequate data from postmortem examinations on these patients to tell exactly what type of displacement of the heart occurs as a result of this form of treatment. Probably both displacement of the heart as a whole and rotation of the heart cause these changes. From the experimental work previously done to produce electrocardiographic changes and because of the lack of consistent QRS changes, one cannot even theorize as to the altered conditions in the thoracic cavities of these patients with any degree of accuracy. It must be sufficient for the present to say that there is obviously some altered relation of the heart to the wall of the chest, the diaphragm and the posterior muscle mass and that the conduction of the action current from the heart to these structures, on which the configuration of the electrocardiogram depends, has been changed.

#### CONCLUSIONS

1 From a study of 84 patients with various types of neoplasms and 1 with tuberculosis of mediastinal lymph nodes who were carefully observed to determine the effect of roentgen therapy on the heart there is no evidence that the heart is affected by roentgen radiation as used at present.

2 The depression of the blood pressure during and after roentgen therapy is probably due to (1) insufficient nourishment, (2) anemia, (3) fever, (4) neoplastic toxemia, (5) general radiation effect and (6) possibly absorption of split protein products.

3 A carotid sinus syndrome may be induced by cervical metastatic disease and will respond to the usual therapy.

4 Adhesive or constrictive pericarditis may occur following severe radiation pleuropulmonitis complicated by infection.

5 Cardiac arrhythmia when present may be expected to respond to the usual therapy.

6 A sequence of changes is observed in electrocardiograms made before, during and after roentgen therapy.

# CLINICAL SIGNIFICANCE OF GLYCOGEN CONTENT OF LIVER

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The importance of the concentration of glycogen in the liver in patients suffering from a variety of clinical disturbances is generally acknowledged. In some instances glycogen impoverishment plays a greater role than in others, but in no case is a glycogen-poor liver without clinical significance, for there is no question that glycogen is one of the organism's greatest assets and that when impoverishment of this substance occurs a great liability results. It is thus obvious that a measure of the hepatic glycogen may be of real clinical significance. However, methods for quantitative measurement of glycogen *in vivo* still do not exist.

The purpose of this paper is to present an indirect procedure for the quantitative estimation of hepatic glycogen "reserve" and to indicate the significance of data obtained by this method in various clinical states.

There is ample evidence that a diminution of glycogen in the liver is probably the essential stimulus to the onset of ketone formation by that organ. A decrease in the glycogen content of the liver means that the amount of carbohydrate available for oxidation by the liver is reduced. There is thus a deficient amount of carbohydrate available for the energy requirements of the organ itself. Since the liver is much more active than any other tissue in the body, it must obtain energy from some source other than carbohydrate and it begins to use protein and fat. Hence a compensatory acceleration in the breakdown of fat and protein occurs. This increased breakdown of fat and protein then results in formation of ketone bodies and dextrose. Acetone bodies are normal products of fatty acid oxidation in the liver,<sup>1</sup> and they appear in excessive amounts in the blood stream only when their rate of production exceeds their rate of oxidation by the tissues.

It is evident that the rapidity with which a liver may be depleted of glycogen is dependent to a great degree on the amount of glycogen present in that organ. Hence a measure of the ability of the liver to maintain its glycogen store should serve as an index of the rapidity with which acetone body formation may occur. Thus, a determination of hepatic glycogen reserve would serve as a gauge of the patient's susceptibility to ketosis.

In 1853 Claude Bernard found that the blood flowing from the liver of a fasting or a meat-fed animal contained sugar, while the blood entering that organ contained none. This led him to conclude that sugar is produced and secreted by the liver. In 1857 Bernard isolated glycogen from the liver, and demonstrated it to be the immediate precursor of the sugar liberated by this organ. Furthermore, he found that glycogen could arise from noncarbohydrate sources. Since that time it has been adequately demonstrated that the liver is the only organ capable of secreting sugar into the circulation and that its ability to maintain the blood sugar level successfully is dependent on its glycogen content. In the normal organism an excessive loss of sugar from the blood stream will stimulate the secretion of sugar by the

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1 Mirsky, I. A. The Source of the Blood Acetone Resulting from the Administration of the Ketogenic Principle of the Anterior Hypophysis, *Am J Physiol* **115** 424, 1936.

liver and the blood sugar level will not change significantly.<sup>2</sup> However, if the liver is poor in glycogen it will not be able to compensate adequately for the loss of sugar from the blood stream and hypoglycemia will result. Furthermore, if the liver has a low glycogen content and uses this to compensate for a loss of sugar from the blood, it will become further impoverished and consequently will draw on fat and protein for energy, with the formation of acetone bodies as one of its products. It is thus obvious that when acetone bodies appear in the blood stream the hepatic glycogen has reached a minimal value.

These considerations have enabled a procedure to be devised whereby quantitative measurement of the glycogen content of the liver in man is made possible. If the renal threshold for sugar is lowered by means of administration of phlorhizin, an increased drain on the blood sugar and thereby on the glycogen reserve of the liver is produced. In instances in which the glycogen content is normal the loss of sugar from the blood stream by way of the kidneys produces no significant change in the blood sugar level. On the other hand, in conditions in which the hepatic glycogen content is known to be inadequate the excretion of a similar amount of sugar results in a definite diminution of the blood sugar. In addition to the drop in blood sugar there may develop simultaneously a ketonemia. This serves as an index of hepatic glycogen impoverishment and suggests that the excreted sugar is all that the liver contained.

Phlorhizin is a glucoside extracted from the root cortex of apple, cherry, plum and pear trees. On hydrolysis it yields dextrose and phloretin. When phlorhizin or phloretin is administered parenterally, it gives rise to glycosuria. Phlorhizin produces a temporary inhibition of reabsorption of sugar in the renal tubules and permits the sugar which is constantly being filtered through the glomeruli to be excreted. The excessive loss of sugar in the urine results in a rapid depletion of hepatic glycogen just as occurs in hyperthyroidism and in insulin deficiency. When the hepatic glycogen is depleted in consequence of the loss of sugar from the blood, the oxidation of fat and protein is accelerated and an increased excretion of urinary nitrogen and acetone bodies ensues. If the phlorhizinized animal is fed adequate amounts of carbohydrate, there occurs an immediate cessation of ketosis and a decrease in protein metabolism.<sup>3</sup>

#### PROCEDURE

This report is based on the results obtained in a study of 155 subjects, of whom 89 were children and 66 were adults. They were divided into three classes: (1) normal, healthy persons, (2) patients with diabetes mellitus of various degrees of severity, (3) patients with hepatic disease (alcoholic or toxic hepatitis, cirrhosis, obstructive jaundice, hepatomegaly or metastatic disease of the liver).

With the exception of the children and of the adults suffering from hepatic dysfunction, each of the classes was divided into a group which received pretreatment with carbohydrate the evening before the test was performed, and another which received no pretreatment.

The children were divided into three groups: (1) those receiving pretreatment the evening before the test, (2) those receiving pretreatment early in the morning on the day of the test, (3) those receiving no pretreatment.

All adults suffering from hepatic dysfunction received pretreatment. Diabetic patients were permitted to take insulin up to the day of the test. In no case was insulin administered on the morning on which the test was performed.

2 Soskin, S. Muscle Glycogen as a Source of Blood Sugar, *Am J Physiol* **81** 382, 1927. Soskin, S., Essex, H. E., Herrick, J. F., and Mann, F. C. The Mechanism of Regulation of the Blood Sugar by the Liver, *ibid* **124** 558, 1938.

3 Chambers, W. H., and Deuel, H. J., Jr. Metabolism of Glycerol in Phlorhizin Diabetes, *J Biol Chem* **65** 21, 1925. Deuel, H. J., Jr., Ellis, H., Wilson, C., and Milhorat, A. T. On the Mechanism of Phlorhizin Diabetes, *ibid* **74** 205, 1927. Soskin, S., Levine, R., and Lehmann, W. Utilization of Carbohydrate by the Phlorhizinized Dog, *Proc Soc Exper Biol & Med* **39** 442, 1938.

Pretreatment with carbohydrate consisted of oral administration of orange juice and cane sugar in an amount sufficient to furnish 2 Gm of carbohydrate per kilogram of body weight. In those instances in which pretreatment was given the evening before the test this mixture was taken at 9 p m. In those in which it was administered on the morning of the test it was given to the subject at 3 a m.

The procedure was as follows. The subject was given his regular evening meal on the day before the test. No food was allowed that night, with the exception of pretreatment when this was administered. As already mentioned, one group of subjects received carbohydrate at 9 p m on the evening before, while another group was given the orange juice-cane sugar mixture at 3 a m on the morning of the test. Breakfast was omitted, and no food was permitted during the test, which was begun between 7 and 7:30 a m and lasted for six hours, however, water, tea or black coffee with saccharin was allowed *ad libitum*. A sample of blood was drawn at the beginning and again at the end of the six hour period and was analyzed for sugar content by the Somogyi modification of the Shaffer-Hartmann method and for total ketones by a modification of the Van Slyke and Fitz method. Immediately after drawing of the first blood sample, 1 Gm of phlorhizin dissolved in tenth-normal sodium hydroxide solution was injected intravenously. The subject then emptied his bladder completely. Since the injected phlorhizin was excreted fairly rapidly, it was found necessary to administer a second 1 Gm dose of phlorhizin intravenously at the end of three hours in order to maintain an adequate glycosuria. The urine was collected during the six hour period, and the total amount of sugar excreted was determined. As previously stated, a second sample of blood was drawn at the end of the six hour period.

### RESULTS

The data obtained in this study are summarized in tables 1 to 5. An analysis of the data may best be made as follows: (1) changes in blood sugar, (2) glycosuria, (3) loss of sugar from the liver, (4) ketosis.

TABLE 1—*Influence of Phlorhizin on the Hepatic Glycogen Reserves of Normal Adults*

Subject No	Age	Sex	Weight, Kg	Initial Blood Sugar, Mg / 100 Cc	Fall in Blood Sugar, Mg / 100 Cc	Dextrose Excreted in Urine, Gm	Total Decrease in Free Sugar, Mg / Kg	Loss from Liver, Mg / Kg	Rise in Blood Ketones Mg / 100 Cc
				Dinner at 6 P M	Nothing	Thereafter			
16	24	M	82.0	55	11	34.0	33	455	0
39	32	M	76.3	74	1	23.3	3	302	0
2	32	M	76.3	87	14	24.2	42	359	0
7	45	M	45.4	65	15	10.9	45	285	0
8	56	M	71	81	1	17.3	3	241	0
9	41	F	51	58	1	12.5	3	248	0
14	63	I		90	9	17.4			0
15	50	F		66	0	17.7			0
81	29	F		84	0	17			0
Dinner at 6 P M, 2 Gm Carbohydrate per Kg. at 9 P M									
94	60	M	45.4	88	6	14.0	18	290	0
68	44	M	74.6	81	7	23.0	21	287	0
32	60	M	66	75	1	14.0	12	200	0
33	60	M	66	74	1	22.3	3	341	0
27	19	M		19	7	15.0			0
34	36	M		66	4	21.9			0
37	49	M		63	10	20.1			0
38	33	M		62	18	21.7			0
44	37	M		90	4	26.5			0
46	40	M		99	9				0
50	26	M		82	0	28.0			0
51	27	M		76	5	26.0			0
150	38	M	70.0	88	2	6.4	6	85	0
91	37	F	57.7	87	10	15.5	30	239	0
41	26	F	49.5	61	1	22.0	3	437	0
40	25	F		78	6	19.9			0

1 *Changes in Blood Sugar*—Table 6 summarizes the findings in the various groups. It is obvious that the administration of carbohydrate to normal adults at 9 p m on the evening before had no significant influence on the changes in the

blood sugar consequent to administration of phlorhizin. The average change in the blood sugar is relatively insignificant and within the limits of experimental error.

In the adult diabetic group a pronounced drop in blood sugar level occurred irrespective of whether or not the patients were pretreated with carbohydrate the night before. Thus, whereas in the normal group the blood sugar decreased by 3 per cent after administration of phlorhizin, a decrease of 46 per cent occurred in the diabetic groups.

The findings in normal children differ decidedly from those in adults. Thus the nonpretreated group had a drop of 23 per cent in the blood sugar level consequent to administration of phlorhizin, as compared with a 5 per cent rise in adults. Furthermore, it is of importance to note that the children given carbohydrate at

TABLE 2—*Influence of Phlorhizin on Hepatic Glycogen Reserves of Diabetic Adults*

Subject No	Age	Sex	Weight, Kg	Initial Blood Sugar, Mg / 100 Cc	Fall in Blood Sugar, Mg / 100 Cc	Dextrose Excreted in Urine, Gm	Total Decrease in Free Sugar, Mg / Kg	Loss from Liver, Mg / Kg	Rise in Blood Ketones, Mg / 100 Cc
				Dinner at 6 P M	Nothing	Thereafter			
69	60	M	66.4	151	29	28.0	87	335	0
17	60	M	62.7	42		9.6	9	144	0
18	72	M	45.4	162	115	18.5	345	63	17.3
21	65	M	44.5	104	52	21.2	156	323	12.6
19	17	M		210	77	42.5			2.6
21	52	M		203	103	33.7			3.1
31	47	M		204	77	43.4			0
3	63	M		259	159	22.4			13.4
10	62	M	72	169	102	14.5	306		0
73	28	F	43.2	89	29	16	87	283	10.5
1	47	F	60	84	29		87		15.5
Dinner at 6 P M, 2 Gm Carbohydrate per Kg at 9 P M									
67	53	M	48.6	338	202	52.0	606	464	23.5
123	24	M	52.3	93	9	15.8	27	275	0
124	61	M	55.5	231	94	39.5	282	430	0
76	45	F	78.2	141	33	25.0	99	221	0
36	22	F	47.2	194	103	24.9	324	204	6.3
63	62	F	71.1	282	112	21.0	336	41	0
61	52	F	45.5	156	47	23.9	141	385	0
43	51	F	52.3	261	161	37.3	483	230	13.7
45	50	F	56.8	270	171	54.0	513	437	9.8
28	17	F		121	79	22.0			7.1
53	51	F		214	117	29.0			0
54	52	F		218	110	28.0			0

9 p m had a smaller decrease in blood sugar, while those given carbohydrate at 3 a m had no change.

The diabetic children all had a marked decrease in blood sugar. This decrease is much greater than that observed in the adult diabetic patients. The administration of carbohydrate the night before appears to have only a slight effect in inhibiting the decrease which follows administration of phlorhizin.

These data reveal that the diabetic subjects invariably showed a decrease in blood sugar concentration consequent to administration of phlorhizin. Of interest is the fact that the majority of these patients were under good clinical control as far as their diabetic status was concerned and that nevertheless great differences were noted as compared with the nondiabetic group.

Patients suffering from a variety of hepatic disturbances revealed a drop in blood sugar consequent to administration of phlorhizin even though the initial level was normal. In this respect these patients behaved like normal children.

2 *Glycosuria*.—The excretion of dextrose varies greatly from patient to patient and from group to group. Reference to tables 1 to 5 clearly demonstrates not only that differences in body weight play a role in the variations in sugar excretion but



that age and clinical status are important factors. In view of the many variables which determine the amount of sugar excreted consequent to administration of phlorhizin, no attempt to compare the various groups on the basis of total dextrose excretion will be made. Generalizing, normal adults excreted approximately 25 Gm in six hours, while normal children excreted approximately 10 Gm in six hours.

TABLE 3—*Influence of Phlorhizin on Hepatic Glycogen Reserves of Normal Children*

Subject No	Age	Sex	Weight, Kg	Initial Blood Sugar, Mg / 100 Cc	Fall in Blood Sugar, Mg / 100 Cc	Dextrose Excreted in Urine, Gm	Total Decrease in Free Sugar, Mg / Kg	Loss from Liver, Mg / Kg	Rise in Blood Ketones, Mg / 100 Cc
Dinner at 6 P M, Nothing Thereafter									
136	14	M	43.6	78	12	17.8	36	372	2.1
137	14	M	54.1	77	3	19.4	9	349	0
138	14	M	50	00	17	23.8	51	425	2
139	13	M	46.8	117	40	22.5	120	361	0
140	13	M	38.2	76	18	14.8	54	333	10.1
141	13	M	40	74	10	14	30	320	0
142	13	M	42.3	82	7	24	21	546	0
143	14	M	47.3	84	12	23.9	36	469	0
78	4	M	14.8	71	14	9	42	566	17.1
80	8	M	25.5	118	55	10	165	227	14.6
83	6	F	18.9	77	1	10	39	490	9.9
85	12	F	53.6	90	23	21	69	323	0.6
86	11.5	F	33.5	80	15	14	45	381	0
87	9	F	23.3	89	24	11	72	422	6.5
74	14	F	67.7	86	25	24	75	280	0
Dinner at 6 P M, 2 Gm Carbohydrate per Kg at 9 P M									
57	13	M	52.3	84	5	21	15	386	0
60	8	M	25	86	11	14	33	527	0
65	11	M	33.6	85	2	15	6	440	0
98	5	M	19.1	84	6	9.6	18	484	7
99	10	M	32.5	87	8	13.2	24	382	0
100	5	M	20.0	90	23	11.3	69	471	8
103	13	M	39.6	90	3	18.5	9	458	2.2
105	14	M	46.8	91	11	15.6	33	304	0
106	13	M	51.4	85	17	23.6	51	408	0
48	12	M	38.6	81	5	15.8	15	425	0
92	4	M	14.7	82	23	15.1	69	958	13.3
114	5	M	16.4	87	18	10.4	54	580	7.4
56	12	F	42.3	73	0	19	0	449	0
89	11	F	33.3	91	3	18.7	9	553	0
96	12	F	45.9	85	7	27.1	21	569	0
97	16	F	70.4	91	0	21.1	27	792	0
101	8	F	25.5	95	20	16.4	60	592	6.1
107	14	F	53.4	70	2	20.6	6	392	0
108	13	F	57.8	73	2	16.3	6	276	0
109	11	F	30	82	18	12.6	54	366	3
110	12	F	32.5	88	15	19.8	45	564	0
112	8	F	21.1	76	22	9.3	66	375	10.6
113	9	F	28.9	82	15	11.8	45	363	0
117	9	F	23.4	90	11	13.4	33	539	0
118	11.5	F	34.2	82	8	16.4	24	456	0
Dinner at 6 P M, 2 Gm Carbohydrate at 3 A M									
121	12	M	42.5	49	21	17.0	93	514	0
122	12	M	38	65	13	20.2	39	571	0
125	13	M	37.8	86	13	17.1	39	413	0
126	15	M	49.5	78	0	20	0	444	0
127	10	M	35.6	75	4	16	12	437	0
128	13	M	50.9	85	10	24	30	441	0
129	10	M	31.8	83	9	13.7	27	404	0
130	9	M	30	77	8	15.3	24	486	0
131	9	M	28.4	80	5	13.4	15	457	0
132	9	M	29.1	71	0	13.6	0	467	0
134	14	M	47.7	71	11	21.5	33	484	0
135	13	M	43	68	7	18.6	21	453	0

3 *Loss of Sugar from the Liver*—Another comparison is permissible. The dextrose that appears in the urine consequent to administration of phlorhizin is excreted from the blood stream. The sugar in the blood stream is in turn secreted by the liver, where it takes origin from the glycogen present in that organ. In order to compute what proportion of the excreted sugar has taken origin from

hepatic glycogen, it is necessary to take into account the over-all changes in the blood sugar

In instances in which the blood sugar reveals no change, all the sugar that appears in the urine must have come from the liver. On the other hand, if the over-

TABLE 4—*Influence of Phlorizin on the Hepatic Glycogen of Diabetic Children*

Subject No	Age	Sex	Weight, Kg	Initial Blood Sugar, Mg / 100 Ce	Fall in Blood Sugar, Mg / 100 Ce	Dextrose Excreted in Urine, Gm	Total Decrease in Free Sugar, Mg / Kg	Loss from Liver, Mg / Kg	Rise in Blood Ketones, Mg / 100 Ce
Dinner at 6 P M, Nothing Thereafter									
72	16	M	51.4	155	101	23	308	144	3.5
75	6	F	23.6	167	127	11	381	85	10.7
82	10	F	38.6	375	273	37	819	139	3.3
84	12	F	38.4	246	187	39	561	455	6.4
Dinner at 6 P M, 2 Gm Carbohydrate per Kg at 9 P M									
52	16	M	54.5	305	155	63	465	691	0
53	7	M	28.6	448	192	52	576	1,242	15
62	15	M	47.7	318	249	48	747	260	0
70	11	M	32.7	305	178	53	534	1,085	7.3
102	16	M	47.8	234	175	29.6	525	94	0
119	11	M	31.8	366	245	48.1	735	777	7.3
55	15	F	39.5	154	87	29	261	425	0
59	10	F	28.1	248	149	35	447	653	11.5
64	12	F	51	361	233	74	699	1,175	19
93	6	F		91	45	10.9	135	253	3.7
49	14	F		166	97	24.2	201	182	0
Dinner at 6 P M, 2 Gm Carbohydrate per Kg at 3 A M									
133	16	M	56.4	392	247	98.3	741	1,002	1.7
144	15	M	51	343	259	57.5	777	350	0
146	6	M	20	306	217	24.9	651	594	12.3
149	15	M	41.4	420	318	59.5	954	483	5.7
152	12	M	40	292	153	49.4	459	776	8.1
145	11	F	40	477	382	45.7	1,146	0	0
148	15	F	53.6	461	303	92.3	924	793	6
151	15	F	53.4	552	241				11.2
153	16	F	56.6	346	196	80.4	588	832	0
154	15	F	51.8	381	307	57.1	921	181	0
155	15	F	43.9	415	319	64	957	501	0

TABLE 5—*Influence of Phlorizin on the Hepatic Glycogen Reserves of Adults with Hepatic Dysfunction*

Subject No	Age	Sex	Weight, Kg	Initial Blood Sugar, Mg / 100 Ce	Fall in Blood Sugar, Mg / 100 Ce	Dextrose Excreted in Urine, Gm	Total Decrease in Free Sugar, Mg / Kg	Loss from Liver, Mg / Kg	Rise in Blood Ketones, Mg / 100 Ce
Dinner at 6 P M, 2 Gm Carbohydrate per Kg at 9 P M									
13	50	M	60	65	6	16.3	18	290	0
20	30	M	86.4	77	54	10	162	997	0
12	39	M	63.1	85	15	18.9	45	255	0
4	46	M		107	38	21.6			8.9
6	41	M		82	27				0
115	43	M	73.6	119	28	17	84	147	0
111	19	F	50	81	12	19.1	36	346	0
23	30	F	50	75	30	13.1	90	172	7.7
22	25	F		53	21	10.3			24.5
95	65	M	55.9	89	13	18.3	39	288	0
26	32	M		80	31	20.8			0
29	50	M		62	12	7.5			0
30	46	M		65	23	5.4			0
35	42	M		70	18	25.2			0
147	38	M	68.4	97	14	21.3	42	270	0
42	68	F	51.8	79	13	9.7	39	148	0

all change in blood sugar is a rise, it is obvious that less sugar has appeared in the urine than left the liver. Hence, in order to determine how much sugar left the liver it is necessary to compute the actual amount of sugar causing the rise in blood sugar concentration and to add that to the amount excreted in the urine. If the

over-all change of the blood sugar shows a fall in level, the amount of sugar excreted in the urine is equal to the sum of that secreted by the liver and that coming from the blood in consequence of the decreased concentration of blood sugar

In order to make these calculations it becomes essential to determine the significance of a change in the blood sugar in terms of the body as a whole. Various values for the mixing volume for distribution of sugar in the body are to be found in the literature. These vary from 18 to 50 per cent of the total body weight. A value of 30 per cent has been found to approximate closest to the true mixing volume (Darrow, 1935, Blatherwick, 1935). With this distribution factor it becomes possible to compute a change in blood sugar in terms of milligrams of dextrose per kilogram of body weight. Thus, for example, the patient in case 2 weighing 76.3 Kg, had a rise of blood sugar of 14 mg per hundred cubic centimeters at the end of the six hour interval. This was calculated to mean a rise of 0.14 mg per cubic centimeter of blood, or 42 mg of dextrose per kilogram of body weight, i. e., 30 per cent of 1 Kg  $\times$  0.14. Since this patient excreted 24 Gm of sugar during the experimental period, the excretion in the urine per

TABLE 6—Changes in Blood Sugar in the Various Groups

Group	Pre treatment	Blood Sugar		
		Initial, Mg per 100 Cc	Final, Mg per 100 Cc	Per Cent of Change
Normal adults	None	74	77	+ 5
	At 9 p m	75	69	- 8
Average		75	71	- 3
Diabetic adults	None	164	92	-43
	At 9 p m	210	100	-50
Average		187	100	-46
Normal children	None	86	66	-20
	At 9 p m	84	74	-12
	At 3 a m	74	75	+ 1
Diabetic children	None	236	64	-73
	At 9 p m	272	118	-60
	At 3 a m	332	117	-64
Adults with hepatic dysfunction	At 9 p m	81	60	-28

kilogram of body weight was 317 mg. In view of the fact that the liver was responsible for the addition to the mixing volume of 42 mg of dextrose per kilogram, the total loss from the liver was  $42 + 317$  mg of sugar per kilogram of body weight. On the other hand, the patient in case 82, weighing 38.6 Kg, showed a drop in blood sugar of 273 mg per hundred cubic centimeters at the end of the experimental period. This was calculated to mean a drop of 2.73 mg per cubic centimeter of blood, or 819 mg per kilogram of body weight, i. e., 30 per cent of 1 Kg  $\times$  2.73. Since this patient excreted 37 Gm of sugar during the six hour interval, the excretion in the urine was 958 mg per kilogram. Thus the secretion of extra sugar by the liver during the experimental period was  $958 - 819$  or 139, mg of sugar per kilogram of body weight.

Computing the data as just outlined, it is possible to compare the different groups on the basis of the amount of extra dextrose secreted by the liver during the experimental period (table 7).

It is of importance to emphasize that the figure designated as "loss of sugar from the liver" represents not the total amount of glycogenolysis but merely the additional breakdown consequent to the increased excretion of sugar in the urine. Thus it may be noted that the normal adults secreted from the liver an extra 49 mg per kilogram of body weight per hour. A similar figure is obtained for the adult

diabetic group Although both groups secreted the same amount of extra sugar from the liver during the experimental period, only the normal group was able to maintain the blood sugar at its original level, the diabetic group had a decided drop in blood sugar concentration The obvious implication of this finding is that there was not enough glycogen present in the persons with diabetes to permit adequate maintenance of their blood sugar level In support of this view are the findings which will be discussed under the heading of ketosis

Of interest is the observation that the rate of the extra glycogenolysis consequent to the increased glycuresis in the normal children was very rapid as compared with that of normal adults The livers of the normal nonpretreated children secreted an average of approximately 100 mg of sugar per kilogram more than the livers of the normal adults during the six hour period The administration of carbohydrate to children results in a greater availability of glycogen, as is indicated by the fact that glycuresis induces a still greater loss from the liver while the blood sugar tends to fall little or not at all

TABLE 7—*Loss of Dextrose from Liver and Development of Ketosis in Various Groups*

Group	Pre treatment	Loss from Liver, Mg /Kg	Ketosis, per Cent of Cases
Normal adults	None	315	0
	At 9 p m	263	0
Average		292	0
Diabetic adults	None	230	64
	At 9 p m	299	41
Average		265	52
Normal children	None	391	53
	At 9 p m	463	36
	At 3 a m	404	0
Diabetic children	None	206	100
	At 9 p m	621	55
	At 3 a m	613	55
Adults with hepatic dysfunction	At 9 p m	324	19

The diabetic children had a large secretion of extra sugar from the liver This demonstrates the ease with which it is possible to accelerate glycogenolysis in children

Patients suffering from hepatic dysfunction likewise had a large secretion of extra sugar from the liver These findings differ from those for diabetic adults in that here more glycogen is available in the liver and hence the amount of glycogen breakdown is greater

This method of analysis permits a comparison between the groups However, the significance of the data becomes apparent only when they are correlated with the changes in blood sugar and the development of ketosis

4 *Ketosis*—The data concerning the development of ketosis are detailed in tables 1 to 5 Since, as was pointed out in the introduction, ketosis develops only when the concentration of glycogen in the liver is at a minimum, it is not considered of importance at this point to discuss the actual amounts of ketone bodies developed during the experimental period For analytic purposes it is of greater interest to determine the percentage of cases in which ketosis developed, since the appearance of 1 mg of acetone bodies in the blood stream is as significant as is the appearance of a larger amount

Reference to table 7 reveals that ketosis did not develop in the normal adults even though their hepatic glycogen stores were deprived of the same amount of

sugar as were those of the diabetic adults. Thus, when 292 mg of sugar per kilogram was removed from the livers of the normal adults ketosis did not develop, whereas after removal of 265 mg of sugar per kilogram of body weight from the livers of the diabetic adults, ketosis developed in 52 per cent of them.

It is of interest to emphasize the fact that normal children receiving dinner at 6 p. m. and no carbohydrate thereafter not only lost a greater amount of sugar from the liver during the experimental period than did normal adults and showed a fall in blood sugar but also had ketosis. In 53 per cent of the children receiving no pretreatment ketosis developed. On the other hand, when additional carbohydrate was administered at 9 p. m., more glycogen thus being made available, only 36 per cent of these children revealed a ketonemia, while the group as a whole had a greater loss of sugar from the liver and a smaller drop of blood sugar. When

TABLE 8—*Relation Between Presence of Ketosis and Change in Sugar Content of Blood and of Liver*

Normal adults	{ Insignificant change in blood sugar No ketosis 292 mg. sugar per kilogram from liver
Diabetic adults	{ Marked fall in blood sugar Ketosis in 52 per cent of cases 265 mg. sugar per kilogram from liver
Normal children given no pretreatment	{ Moderate fall in blood sugar Ketosis in 53 per cent of cases 391 mg. sugar per kilogram from liver
Normal children pretreated at 9 p. m.	{ Slight fall in blood sugar Ketosis in 36 per cent of cases 468 mg. sugar per kilogram from liver
Normal children pretreated at 3 a. m.	{ No change in blood sugar No ketosis 464 mg. sugar per kilogram from liver
Diabetic children given no pretreatment	{ Marked drop in blood sugar Ketosis in 100 per cent of cases 206 mg. sugar per kilogram from liver
Diabetic children pretreated	{ Marked drop in blood sugar Ketosis in 55 per cent of cases 617 mg. sugar per kilogram from liver
Adults with hepatic dysfunction	{ Marked drop in blood sugar Ketosis in 19 per cent of cases 324 mg. sugar per kilogram from liver

normal children received carbohydrate at 3 a. m., ketosis did not develop, nor was there any drop in blood sugar.

The findings are entirely different in the group of diabetic children. Those who received no extra carbohydrate secreted a relatively smaller amount of dextrose from the liver, and all of them revealed ketosis. The administration of carbohydrate to the diabetic children made available a greater amount of glycogen for subsequent breakdown, as indicated by the loss from the liver, and resulted in a reduction in incidence of ketosis to 55 per cent.

The studies with the adult group suffering from various hepatic dysfunctions reveal that ketosis developed in 19 per cent of the patients at the same time that a drop in blood sugar and an increase in glycogenolysis occurred.

A clearer picture of our findings becomes apparent when the different groups are compared in terms of all the data, as in table 8.

#### COMMENT

Although opinions differ as to the exact mechanism responsible for the syndrome of diabetes mellitus, unanimity exists with regard to the fact that in

this condition the hepatic glycogen is decreased. When the glycogen falls to a certain minimal level, oxidation of fat is accelerated and ketosis ensues. Since ketosis is the major factor responsible for the development of diabetic coma, it is obvious that any measure of the susceptibility to ketosis can serve also as an index of susceptibility to coma. Since the latter is really the most important single factor indicative of severity of diabetes, it is obvious that the aforementioned "measure" would serve also as an index of diabetic severity.

If excretion of sugar via the kidneys is accelerated, the blood sugar will remain level so long as an adequate amount of glycogen is present in the liver. If an adequate amount of glycogen is not present in that organ, the blood sugar will fall until the rate of hepatic secretion is equal to the rate at which sugar is lost from the blood stream. Thus a measure of the glycogen reserve of the liver may be obtained.

It may be argued that the extra dextrose which is excreted in the urine consequent to administration of phlorhizin may be due to gluconeogenesis. In order to obviate this criticism, an experiment was performed in which the hourly excretion of nitrogen was studied before and after the injection of phlorhizin. No change whatsoever occurred in nitrogen excretion, even though an increased glycuresis took place.

The fact that with the same loss of sugar from the liver ketosis developed in the diabetic adult group but not in the normal adult group suggests strongly that the glycogen reserves of the persons with diabetes were inadequate at the outset of the study. It is apparent that the administration of phlorhizin produces an effect similar to that which any other glycogenolytic agent would induce. That is to say, administration of this glucoside permits one to measure the capacity of the liver to retain carbohydrate in amounts sufficient to prevent ketogenesis and indicates the course of events which might ensue consequent to the development of an infection or other glycogenolytic stimulus.

The clinical consensus is that children are more susceptible to the development of ketosis than are adults. The present study provides quantitative evidence to substantiate this clinical impression. It was found that normal children secrete relatively large amounts of carbohydrate and have a drop in blood sugar and a rise in blood acetone bodies when excretion of sugar is induced. That this is dependent on glycogen reserve is definitely indicated by the fact that in our experiments administration of extra carbohydrate at 9 p. m. or at 3 a. m. resulted in a decreasing ketosis and an inhibition of the tendency toward development of hypoglycemia (tables 6 and 7).

Not only is the glycogenolytic rate greater in the normal child than in the adult, but it is still further increased in the diabetic child, which indicates a still greater susceptibility to ketosis. This may account for the fact that diabetic children are so susceptible to coma and that their diabetic condition is relatively severe. For, starting with an equal concentration of glycogen in the liver, the child will lose this glycogen at a faster rate than the adult, and if diabetes or an infection supervenes, the tendency to ketosis is further augmented.

Of interest is the observation that the younger the child the greater is his susceptibility to ketosis. However, the number of cases available for analysis are too few to permit statistical consideration.

In view of the preceding observations, it may be possible that the methods outlined in this thesis can be utilized for categorizing the severity of diabetes in individual patients, since with a given loss of glycogen from the liver differences in susceptibility to ketosis and in the drop in blood sugar may be noted in these patients. Furthermore, it may be possible to employ this procedure to determine

the presence or absence of latent diabetes. For example, Mrs N L, mother of a diabetic child, had a fasting blood sugar of 89 mg per hundred cubic centimeters and no fasting glycosuria. Six hours after administration of phlorhizin the sugar content of the blood fell to 60 mg per hundred cubic centimeters and 10.5 mg of acetone bodies per hundred cubic centimeters appeared. Calculation revealed that 283 mg per kilogram of extra dextrose was secreted by the liver during the six hour interval. Since a normal patient would secrete a similar amount of sugar without the development of ketosis or hypoglycemia, it is obvious that this patient has a hepatic glycogen impoverishment. Of course it is possible that in such instances one is dealing not with latent diabetes mellitus but with some other hepatic dysfunction. The presence of other stigmas of hepatic dysfunction should determine the diagnosis.

The fact that patients suffering from disturbances of the liver tend to retain relatively small amounts of glycogen is demonstrated in these studies, which also lend support to the evidence obtained in experiments on lower species that glycogenesis and glycogenolysis are disturbed in diseases involving the liver.

#### SUMMARY AND CONCLUSIONS

Administration of phlorhizin and the consequent glycosuria result in removal of circulating sugar. In conditions in which the glycogen reserve of the liver is adequate the blood sugar remains relatively constant. In conditions in which the glycogen reserve is inadequate the blood sugar level drops and ketosis may develop.

The study reveals that diabetic adults do not retain carbohydrate in their livers to the same degree as do normal adults and that removal of relatively small amounts of sugar from their blood stream results in a further deprivation of liver glycogen, with consequent development of hypoglycemia and ketosis.

Children cannot retain carbohydrate to the same degree as do adults, because of an apparent increased rate of glycogenolysis. This is true not only for diabetic children but for normal children and accounts for their susceptibility to ketosis. Administration of carbohydrate to normal children results in a greater deposition of glycogen in the liver, so that their reserve is increased and their susceptibility to ketosis decreased.

Patients suffering from hepatic dysfunction have an inadequate glycogen reserve.

The possibility is suggested that the method outlined may be of value in categorizing diabetic severity.

Medical Arts Building

# CARDIOVASCULAR MANIFESTATIONS IN PERNICIOUS ANEMIA

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Profound circulatory changes occur in both primary and secondary anemia

With a decrease in the hemoglobin content of the blood the output of the heart is increased<sup>1</sup> This is the outstanding compensatory mechanism for the loss of oxygen-carrying power of the blood The cardiac rate is also increased in anemia<sup>2</sup> Although the cardiac acceleration is moderate, rarely more than 120 per minute, it results in a certain increase in cardiac output This increase in minute volume output is due, likewise, in part, to lowering of the viscosity of the blood<sup>1c</sup> Nevertheless, the increased cardiac output observed in anemia is due mainly to the increased systolic output of the heart This increase in cardiac output is directly proportional to the decrease in hemoglobin content of the blood A 200 per cent and a 300 per cent increase are reported to occur with hemoglobin levels of 30 per cent and 20 per cent respectively, the cardiac output being normal when the hemoglobin content of the blood is 50 per cent or more<sup>3</sup>

Reasons for this augmented cardiac output in anemia have been given<sup>2a</sup> In blood with a 100 per cent hemoglobin content, 55 of the 18 volumes of oxygen is utilized by the tissues If only 55 volumes of oxygen should be available (corresponding to a hemoglobin of 30 per cent), there being no reserve, the oxygen pressure would fall to zero (which occurs only in death) unless some compensatory mechanism intervened In this event, the patient would be incapable of muscular effort In carbon monoxide poisoning coma or death follows when only 30 per cent of free hemoglobin remains, the gas being harmful only so far as it prevents oxygenation by combining with the hemoglobin

Considering the chronicity of pernicious anemia, some mechanism of compensating for the deficit of hemoglobin and the resultant decrease in oxygenation must exist The increased cardiac output represents this compensatory mechanism The

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fewer erythrocytes, by moving with increased velocity, make their oxygen-carrying capacity more frequently available. This mechanism is essential for the satisfactory oxygenation of tissue in the presence of a definitely lowered hemoglobin content of the blood.<sup>3c</sup> It leads to changes in the heart.

Cardiac hypertrophy frequent and marked, has often resulted from anemia produced by hemolysis.<sup>2a</sup> Cardiac enlargement in anemia, without other etiologic basis, has been repeatedly observed.<sup>4</sup> The largest heart weighed 710 Gm.<sup>5</sup> The hypertrophy usually involves the two ventricles equally, the heart being symmetrically enlarged.<sup>4a</sup> Such compensation may be transitory. If the blood improves, the heart returns to normal. With a severe, prolonged anemia the deficit becomes chronic and the hypertrophy persists. Decreased oxygenation of the myocardium may then become a factor in provoking failure of the enlarged heart. Absence of cardiac hypertrophy in an anemia of moderate degree is best explained by the fact that the cardiac output is not appreciably augmented until the hemoglobin falls below 50 per cent, the organism functioning satisfactorily so long as the quantity of hemoglobin is not reduced more than one half.

At low hemoglobin levels the stroke volume, the minute volume output, the cardiac rate and the oxygen consumption are increased. The arm to tongue circulation time is decreased. With a rise in the hemoglobin content of the blood these changes are reversed. A rise of systolic and diastolic blood pressure also occurs. In spite of the fact that the shortened circulation time, increased cardiac output, decreased hemoglobin and increased oxygen consumption are so related that an organ already working at an accelerated rate is put to the added disadvantage of maintaining a circulation sufficient for the requirements of an increased basal metabolic rate, some believe (1) that left ventricular work, per beat and per minute, is not increased in anemia, (2) that the work per beat is actually less than when the hemoglobin concentration is normal, (3) that the heart in anemia, at rest and without congestive failure, mechanically performs, commensurately with its size, the work to be expected of it.<sup>3c</sup> It appears that the enlarged heart of anemia is due to anoxemia rather than to increased cardiac work.

Strumpell,<sup>6</sup> in 1886, recognized palpitation as one of the first symptoms of severe anemia, that breathing was hurried due to a feeling of air hunger and shortness of breath and that a feeling of oppression in the breast was characteristic. The prolonged delay in the recognition of the occurrence of angina in anemia seems surprising.<sup>7</sup> Herrick's<sup>8</sup> discussion of 150,<sup>9</sup> 111,<sup>10</sup> 75,<sup>11</sup> 628,<sup>12</sup> 127,<sup>13</sup> 127,<sup>14</sup> 148,<sup>15</sup> 117<sup>16</sup> and 20<sup>17</sup> cases of pernicious anemia recently reported in which the authors made no mention of angina is interesting.

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Long ago Herrick said that "blood of poor quality going through somewhat narrowed coronary arteries, might favor, on slight provocation, the development of an anginal attack"<sup>7</sup> The occurrence of angina in anemia<sup>7</sup> has been repeatedly confirmed<sup>18</sup> The relative infrequency of this syndrome has, likewise, been confirmed<sup>19</sup> Comparatively few patients with angina are found in the many large series of cases of pernicious anemia investigated<sup>20</sup> Many single case reports appear in the literature<sup>21</sup>

The anemic patient may experience dyspnea, dizziness, angina or claudication<sup>2b</sup> With sclerosis of the coronary or limb arteries, activity may provoke angina or claudication Without these symptoms, dyspnea or dizziness may develop Dyspnea or dizziness may so limit the patient's activity as to prevent the occurrence

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19 Herrick<sup>8</sup> Hochrein and Matthes<sup>18f</sup>

20 Bouchut and Froment<sup>2a</sup> Pickering and Wayne<sup>2b</sup> Zimmermann<sup>2c</sup> Coombs<sup>18i</sup> Keefer and Resnick<sup>18b</sup> Reichel<sup>18c</sup> Porter<sup>18d</sup> Wilkinson<sup>18e</sup> Hochrein and Matthes<sup>18f</sup> Paschkis<sup>18g</sup> Bloch<sup>18h</sup> Bloch<sup>2d</sup>

21 Hunter<sup>18j</sup> Sturgis<sup>18k</sup> Conner<sup>18l</sup> Levine<sup>18m</sup> Carey<sup>18n</sup> Witts<sup>18o</sup> Gwyn<sup>18p</sup> Elliott<sup>18q</sup> Beach<sup>18r</sup> Stalker<sup>18s</sup> Vatcher<sup>18t</sup>

of angina or claudication. In other patients, these symptoms being less readily induced, exercise results in angina or claudication, even in the absence of local vascular disease.

The hypothesis of relative myocardial ischemia as the cause of pain in angina, considered by Jenner,<sup>22</sup> Parry<sup>23</sup> and later by Allan Burns<sup>24</sup> and MacKenzie,<sup>25</sup> has been revived.<sup>18b</sup> Recent evidence<sup>26</sup> indicates that the pain of angina and claudication are due to a similar mechanism, a stimulation of nerve endings in the tissue spaces of the active muscles by a chemical or physicochemical change, factor P, representing the accumulation of products formed during muscular contraction and ordinarily removed by oxidation. The increased circulation rate (decreased circulation time) generally accepted as occurring in anemia<sup>3</sup> is not accompanied by an increased flow through the limbs.<sup>27</sup> In fact, during contraction, the blood flow through a muscle is reduced, owing to compression of blood vessels.<sup>28</sup> A great increase in blood flow occurs soon after contraction, thereby providing a supply of oxyhemoglobin adequate to remove "factor P" very quickly, even in the anemic state.<sup>2b</sup> Claudication in anemia has been observed.<sup>29</sup> In a series of 25 cases of severe anemia, 6 of the 7 patients with claudication were free from attacks after control of their anemia.<sup>2b</sup> Claudication occurred once in our series and was relieved by control of the anemia. Cardiac hypertrophy may be a factor in the production of myocardial ischemia. Anemia predisposes to coronary inadequacy during exertion.<sup>30</sup>

A change in the heart rate occurs in anemia.<sup>2</sup> The pain of angina has been closely related to a rise in cardiac rate with its associated increased energy expenditure of the heart.<sup>26c</sup> This rise in pulse rate after exercise is greater in the anemic than in the nonanemic state.<sup>2b</sup> Changes in blood pressure occur in anemia, the pressure, before and after exercise, often being reduced.<sup>31</sup> The coronary circulation is decreased considerably by such a fall in the mean arterial pressure.<sup>32</sup>

The decrease in the supply of oxygen explains the coronary insufficiency occurring in anemia and in carbon monoxide poisoning.<sup>33</sup> Angina in methemo-

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29 Pickering<sup>2b</sup> Bloch<sup>18b</sup> MacKenzie<sup>25</sup>

30 Fahr, G E. Hypertension Heart. The Most Common Form of So-Called Chronic Myocarditis, *J A M A* **80** 981 (April 7) 1923. Elliott<sup>18a</sup>

31 Pickering<sup>2b</sup> Wayne<sup>26c</sup>

32 Anrep, G V, and King, B. The Significance of the Diastolic and Systolic Blood Pressures for the Maintenance of the Coronary Circulation, *J Physiol* **64** 341, 1928.

33 Gotsch, K. Therapie der Myokardschaden, *Med Klin* **32** 275 1936.

globinemia, from benzene poisoning, diagnosed as heart disease has been reported<sup>34</sup> That a severe anemia may inaugurate an angina, particularly in the presence of an existing organic disturbance of the coronary circulation, is recognized Angina may occur in any kind of organic heart disease coincidentally with anemic fluctuations The improvement or complete cessation of angina following transfusion,<sup>35</sup> or anti-anemic therapy,<sup>36</sup> has been recorded In a woman with primary and in one with secondary anemia, angina was so severe that they sought treatment for that reason only<sup>2c</sup> The angina was relieved with control of the disease of the blood Five cases of angina in anemia with normal coronary arteries have been described<sup>37</sup> In most instances angina occurs only when there is some associated coronary disease By lowering the oxygen supply to the heart still further, the anemia reveals, clinically, a permanent limitation of coronary blood flow unsuspected under ordinary circumstances<sup>2b</sup> Many doubt that anemia will initiate an attack of angina without some background of coronary disease, insisting that marked anoxemia does not produce angina if the coronary arteries are functionally and organically sound<sup>38</sup> Angina in youth is rare<sup>18f</sup>

Some believe that an increased vagal tonus alone may cause disturbance in the coronary circulation and that this vagotonia, as well as coronary disease, may initiate angina In coronary sclerosis a rise in tonus may be due to vasomotor factors<sup>39</sup> The results of lumbar sympathectomy for claudication support this view Thus the cardiovascular manifestations may not be due entirely to anemia with its resultant myocardial anoxemia<sup>40</sup> Cardiac complaints, including angina, may be entirely absent in a form of heart disease predisposed to angina, even in the presence of a severe anemia with necropsy evidence of marked myocardial change due to the anemia<sup>18h</sup> A man of 64 years with a hemoglobin reading of 30 per cent never experienced angina, in spite of extensive coronary sclerosis found at necropsy A full, energetic and prolonged life may be enjoyed in spite of severe anemia<sup>18f</sup>

Reports of 5.5 per cent of 3,400 patients observed over a period of 20 years<sup>41</sup> and 3.45 per cent of 4,000 who came to autopsy<sup>5</sup> probably express the true percentage incidence of angina in older people Disagreement exists as to the frequency of occurrence of angina in anemia Reports of 8 instances in 25 cases,<sup>2b</sup> 8 in 36,<sup>18a</sup> 3 in 370,<sup>18e</sup> 13 in 140<sup>18h</sup> and 43 in 1,560<sup>37</sup> are representative of the variation in the reported incidence of angina in anemia In a report of 113 cases of primary and 327 of secondary anemia, along with 297 cases of angina pectoris, the instances of anemia comprised 1.7 per cent of the cases of angina pectoris<sup>18f</sup>

Severe anemia does not occur often in youth Usually it is due to sudden loss of blood from injury or abortion which confines the patient to bed, the effects of exertion being avoided<sup>2d</sup> Pernicious anemia occurs later in life In 500 cases

34 Schilling, V Die Wechselbeziehungen von Atmung und Kreislauf, Leipzig, Theodor Steinkopff, 1935

35 Willius, F A, and Giffin, H Z The Anginal Syndrome in Pernicious Anemia, *Am J M Sc* **174** 30, 1927 Levine<sup>18m</sup>

36 Pickering<sup>2b</sup> Zimmermann<sup>2c</sup> Bloch<sup>2d</sup> Bloch<sup>18h</sup>

37 Cabot<sup>5</sup> Elliott<sup>18q</sup> Willius<sup>35</sup>

38 von Bergmann, G Funktionelle Therapie, ed 2, Berlin, Julius Springer, 1936 Zimmermann<sup>2c</sup> Levine<sup>18m</sup> Stalker<sup>18s</sup>

39 Romberg, E Ueber Koronarsklerose, *Munchen med Wchnschr* **79** 1021 and 1065, 1932

40 Szerkely, P Electrocardiographic Findings in Anemia, *Brit Heart J* **2.1**, 1940 Goldhammer, S, and Scherf, D Elektrokardiographische Untersuchungen bei Kranken mit Angina pectoris, *Ztschr f klin Med* **122.134**, 1932

41 Edens, E Die Krankheiten des Herzens und der Gefasse, Berlin, Julius Springer, 1929

of angina due to uncomplicated arteriosclerosis the average age of the patients was 65,<sup>42</sup> whereas in series of cases of angina associated with anemia the average ages were from 42.3<sup>2d</sup> to 53.5<sup>35</sup> years. Among persons with the angina of organic heart disease there is a predominance of males, only 25 per cent of 500 patients being females.<sup>42</sup> This is not true of the angina of anemia. Of 250 patients, 85 with primary and 165 with secondary anemia, 82 were males and 168 females, and of the 18 having angina, 5 were men and 13 women.<sup>2c</sup> Of 43 patients with angina among 1,560 anemic patients, 27 were males and 16 were females.<sup>5</sup> Of our 300 patients with pernicious anemia, 163 were males and 137 females. No direct relationship exists between the severity of the anemia and the appearance of angina.<sup>35</sup> Although angina usually occurs with hemoglobin levels of 30 to 40 per cent, nevertheless, in a group of 250 cases 27 of the patients with the most severe anemia (20 having a Sahli reading under 20 per cent and 22 with an erythrocyte count below 1,000,000) had no angina.<sup>2c</sup> The mortality of anemic patients with angina is low, 1 in 13,<sup>18h</sup> 1 in 43,<sup>35</sup> 2 in 4 primary and 2 in 12 secondary anemias.<sup>2c</sup> Contrasting sharply with this, 213 of 500 patients with angina of uncomplicated heart disease died within 4.4 years.<sup>1c</sup>

There is a great possibility of error in attempting to segregate patients with anemia having cardiovascular involvement.<sup>2d</sup> Low mortality and lack of necropsies interfere with the ready exclusion of organic cardiovascular disease in patients with pernicious anemia who have angina. Statistical studies are un dependable. Angina is frequently not recorded or not inquired about by the examiner.

Other cardiovascular complaints are more common than angina and claudication.<sup>43</sup> They are not restricted to any type of anemia and are not related to the severity of the anemia.<sup>10</sup> With dyspnea, an enlarged heart and murmurs the disease frequently gives the appearance of heart disease. In 10 of 36 cases of anemia, the initial diagnosis was heart disease, 6 patients were elderly persons with angina or dyspnea and edema.<sup>18a</sup> Other instances of anemia, mistaken for primary heart disease, have been reported.<sup>14</sup>

In this study an outspoken relationship was noted between cardiovascular complaints and the disease of the blood. With improvement in the condition of the blood the cardiovascular manifestations lessened. Anemia may bring out cardiac symptoms in a patient with involvement of the heart. In 4 of the 6 patients with mitral stenosis, symptoms first developed with the onset of anemia. With improvement of the blood picture, 2 of these were relieved. In the present series, the occurrence of cardiovascular symptoms and findings with hematologic decompensation and their disappearance following treatment or during a remission are striking. Since angina or any other cardiovascular symptom may be the initial or outstanding evidence of severe disease of the blood,<sup>45</sup> these manifestations even when accompanied by such graphic changes as low voltage, displacement of the ST interval or even definite flattening of the T wave, do not necessarily mean primary heart disease. All these signs, the usual criteria of primary cardiovascular disease, may occur solely as the result of severe anemia. Hematologic examination is the only dependable means of differentiation. It is important in angina to rule out anemia as a determining or contributing factor, especially if the angina is

42 White, P. D., and Bland, E. F. A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis. A Study of Five Hundred Cases of the Former Condition and of Two Hundred of the Latter, *Am Heart J* 7 1, 1931.

43 Ellis.<sup>4c</sup> Hochrein and Matthes.<sup>18f</sup>

44 Jagic, N., and Klima, R. *Klinik und Therapie der Blutkrankheiten*, ed. 2, Berlin, Urban & Schwarzenberg, 1934. Schilling.<sup>34</sup> Von Bergmann.<sup>38</sup>

45 Coombs.<sup>18a</sup> Bloch.<sup>18h</sup>

associated with palpitation, dyspnea, enlarged heart, systolic murmur, low arterial pressure, edema or urobilinogenuria. If anemia is present a therapeutic test may be necessary to determine its role in the production of cardiac symptoms.

With acute anoxemia a known cause of such a variety of changes in the electrocardiogram, it is surprising that so few graphic changes have been reported in severe anemia. With "tiger heart" commonly resulting from long-standing anemia and with the anemic heart behaving clinically as though myocarditis were present, this lack of graphic evidence is surprising.<sup>46</sup> In 20,<sup>17</sup> 113,<sup>18f</sup> 12<sup>85</sup> and 15<sup>47</sup> cases of pernicious anemia significant graphic changes were not recorded.

Conduction defects resulting from anemia have long been recognized.<sup>18</sup> In 2 of 10 patients severely ill with anemia, the PR interval was abnormally prolonged. It returned to within normal limits after correction of the anemia (from 0.265 second duration with hemoglobin of 33 per cent to 0.19 second with hemoglobin of 97 per cent and from 0.205 second duration with hemoglobin of 38 per cent to 0.145 second with hemoglobin of 110 per cent).<sup>46</sup> Other graphic changes in anemia have been reported.<sup>46</sup> Displacement of the ST interval simulating that

TABLE 1—*Distribution of Patients According to Age and to Presence of Cardiovascular Manifestations*

Age, yr	Without Cardiovascular Manifestations	With Cardiovascular Manifestations	Total
20-24	0	1	1
25-29	1	5	6
30-34	2	11	13
35-39	1	14	15
40-44	1	20	21
45-49	9	27	36
50-54	9	34	43
55-59	9	46	55
60-64	6	40	46
65-69	2	33	35
70-74	0	21	21
75-79	0	1	1
80-84	0	1	1
Total	43	257	300

of coronary occlusion has been described.<sup>50</sup> Many have described T waves of low amplitude,<sup>51</sup> displacement of the ST interval,<sup>52</sup> and low voltage<sup>51</sup> in anemia, with<sup>18f</sup> and without<sup>63</sup> apparent heart disease.

#### PERSONAL OBSERVATIONS

Inconsistencies in the reported incidence of angina in anemia led us to determine its incidence in a large series of patients. The other symptoms and findings

46 Hochrein and Matthes<sup>18f</sup> Bloch<sup>2d</sup>

47 Smith, K. S. The Nutrition of the Heart in Relation to the Electrocardiogram and Anginal Pain, *Lancet* **1** 632, 1933

48 Lewis, T., and Mathison, G. C. Auriculo-Ventricular Heart-Block as a Result of Asphyxia, *Heart* **2** 47, 1910. Mathison, G. C. The Cause of the Heart-Block Occurring During Asphyxia, *Heart* **2** 54, 1910

49 Zimmermann<sup>2c</sup> Hochrein and Matthes<sup>18f</sup>

50 (a) Dietrich, S., and Schwegk, H. Das Schmerzproblem der Angina pectoris, *Klin Wchnschr* **12** 135, 1933. (b) Kountz, W. B., and Hammouda, M. Effect of Asphyxia and of Anoxemia on the Electrocardiogram, *Am Heart J* **8** 259, 1933. (c) Rothschild, M. A., and Kissin, M. Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, *ibid* **8** 745, 1933. Paschke<sup>18g</sup>

51 Bloch<sup>2d</sup> Bloch<sup>18h</sup>

52 Bloch<sup>2d</sup> Bloch<sup>18h</sup> Elliott<sup>18q</sup> Dietrich<sup>50a</sup> Kountz<sup>50b</sup> Rothschild<sup>50c</sup>

53 Bloch<sup>2d</sup> Bloch<sup>18h</sup> Elliott<sup>18q</sup>

(dyspnea, cardiac enlargement and edema) so overshadowed our original interest that they demanded major consideration

We reviewed the histories of 300 authenticated cases of pernicious anemia from the standpoint of cardiovascular symptoms and findings (table 1). There were 257 with and 43 without cardiovascular manifestations. There were 298 white (99 per cent) and 2 Negro (1 per cent) patients, 163 men (54 per cent) and 137 women (46 per cent). Seventy-four (25 per cent) of the patients died, and necropsy was performed on 6 (2 per cent). No attempt was made to segregate those having primary cardiac disease when the patients were classified according to the presence of cardiovascular manifestations. The incidence of various symptoms and findings in our 300 patients is shown in table 2. Of the 79

TABLE 2—*Symptoms and Findings of Organic Heart Disease*

	Number of Cases	Per Cent		Number of Cases	Per Cent
Angina	3	1	Basal rales	21	7
Precordial pain (nonanginal)	38	12	Edge of liver down	79	26
Weakness	231	77	Liver tenderness	9	,
Dyspnea	154	51	Apical systolic murmur	144	48
Palpitation and tachycardia	66	22	Apical presystolic murmur	5*	1
Dizziness	26	8	Apical diastolic murmur	7	2
Scotomas	13	4	Basal systolic murmur	53	17
Timitus	3	1	Basal diastolic murmur	7	2
Displacement of left cardiac border	87	29	Aortic systolic murmur	31	10
Edema of ankles	104	34	Transmitted murmur	11	3

\* Two of these patients had a presystolic thrill in addition to the murmur

patients showing enlargement of the liver, the edge was below the costal margin 1 cm in 24, 2 cm in 17, 3 cm in 14, 4 cm in 10 and 5 cm in 5, the distance was not recorded for 9 patients. In 54 of the 300 cases the blood pressure was not recorded. In the other 246 cases the readings were as follows:

Pressure	No. of Cases
<100/60	49
<120/80	96
<140/90	60
>140/90	41

The duration of symptoms in 259 cases was as follows (in 41 cases there was no record):

Duration of Symptoms	No. of Cases
1-3 mo	53
3-6 mo	26
6-12 mo	31
1-2 yr	56
2-3 yr	30
3-4 yr	22
4-5 yr	11
5-6 yr	18
7 yr	3
8 yr	1
9 yr	1
10 yr	4
14 yr	1
15 yr	2

The erythrocyte counts were

No of Red Cells	No of Cases
Less than 500,000	3
500,000-1,000,000	90
1,000,000-2,000,000	119
2,000,000-3,000,000	46
3,000,000-4,000,000	16
4,000,000-5,000,000	6
More than 5,000,000	4

No count was recorded on the current chart in 16 cases. These, along with the last 4 cases, were instances of readmission of patients with pernicious anemia. In 212 of the 300 cases the erythrocyte count was below 2,000,000.

The leukocyte counts of 280 patients were normal or decreased proportionately to the decrease in hemoglobin and red cells except in 3 instances. A woman aged 45 with a leukocyte count of 20,400 died of bronchopneumonia on her eighth day in the hospital. A woman aged 70 with cardiac decompensation and an infection of the upper respiratory tract had a leukocyte count of 16,700 just before death. Another woman, aged 76, with organic heart disease and a blood pressure of 194 systolic and 100 diastolic had an unexplained rise of leukocytes to 13,600.

#### CASE HISTORIES

**CASE 1**—A man 44 years old, ill nine months with dyspnea, palpitation, edema of the ankles, enlargement of the heart, an apical systolic murmur, the edge of the liver 1 cm below the costal margin and the blood pressure 140 systolic and 70 diastolic, had been unsuccessfully treated for organic heart disease with decompensation for two months. He had gained 40 pounds (18 Kg). Pernicious anemia was discovered (hemoglobin content 35 per cent, erythrocyte count 1,340,000, color index 1.4 and leukocyte count 3,800). Treatment of cardiovascular decompensation with proper control of the anemia gave prompt relief. The weight returned to normal.

**CASE 2**—A man of 35 years, unable to walk because of changes in the spinal cord, with precordial pain, dyspnea, palpitation, apical and basal systolic murmurs and the edge of the liver 1 cm below the costal margin, had a hemoglobin content of 30 per cent, an erythrocyte count of 1,330,000, a color index of 1.1 and a leukocyte count of 6,700. All abnormalities except the murmurs definitely improved with management of the anemia alone. The patient left the hospital six months later.

**CASE 3**—A man aged 47, ill seven months and treated for heart disease, was admitted to the hospital in coma. His hemoglobin content was 20 per cent, the erythrocyte count 770,000, the color index 1.3 and the leukocyte count 3,100. There were dyspnea, edema of the ankles and an apical systolic murmur. The left cardiac border was 3 cm outside the mid-clavicular line, the edge of the liver was 8 cm below the ribs, and the spleen was felt 2 cm below the umbilicus. Response to injections of liver extract was satisfactory. All symptoms and findings cleared promptly. The patient was discharged on the fifty-seventh day of hospitalization as having made "a remarkable recovery."

**CASE 4**—A man aged 59, ill two years, admitted to the hospital in a second relapse, with a hemoglobin content of 20 per cent, an erythrocyte count of 740,000, a color index of 1.3 and a leukocyte count of 2,540, complained of dyspnea, edema of the ankles and precordial pain of six months' duration. Control of the anemia relieved all symptoms.

**CASE 5**—A man aged 58, with a hemoglobin content of 40 per cent, an erythrocyte count of 1,400,000, a color index of 1.43 and a leukocyte count of 3,700, had anginal pain, dyspnea, edema of the ankles, definite enlargement of the heart, apical and aortic systolic murmurs with fibrillation and a history of rheumatism twenty years previously. He was relieved by treatment of the anemia.

**CASE 6**—A man aged 43, with a hemoglobin content of 30 per cent, an erythrocyte count of 1,260,000, a color index of 1.15 and a leukocyte count of 3,400, had dyspnea, pain in the right side of the chest, edema of the ankles, enlargement of the left side of the heart, an apical presystolic murmur and thrill and an aortic diastolic murmur. He was relieved by management of the anemia.



CASE 7—A man aged 52, ill six months with cardiac failure and definite hematologic decompensation, whose condition appeared terminal on his admission to the hospital, was comfortable after four days of liver therapy. A PR interval of 0.34 second decreased to 0.19 second.

CASE 8—A man aged 61 with mild cardiac and hematologic failure of five years' duration had moderately severe cramps in the muscles of his calves, which disappeared with control of the anemia.

#### SUMMARY

Cardiovascular manifestations were found in 257 of 300 cases of pernicious anemia. In the presence of severe anemia it is impossible to segregate dependably patients with primary cardiovascular involvement. All of the usual criteria of cardiovascular disease may occur solely as the result of anemia. These symptoms and findings are not restricted to any type of anemia or related to the severity of the anemia. Examination of the blood is essential for dependable differentiation. Cardiovascular manifestations often occur with hematologic decompensation and disappear after treatment or during a remission.

# HYPERTENSION IN ONLY ONE OF IDENTICAL TWINS

REPORT OF A CASE, WITH CONSIDERATION OF PSYCHIO-  
SOMATIC FACTORS

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AND

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Because it has been assumed rather generally that the heredity patterns of identical twins are essentially similar, a study of any disease process affecting identical twins is of importance in that it may suggest the presence or absence of heredity factors in the pathogenesis of this particular disease. A study of cardiovascular disease occurring in identical twins may have such pertinence.

Electrocardiographic studies<sup>1</sup> of identical twins have shown that, although the electrocardiograms of identical twins are similar in many instances, they are not always so and may be considerably different.

Rheumatic fever with carditis in each of a pair of identical twins has been reported by Morgan and Webster<sup>2</sup> and by Perry<sup>3</sup>. However, the latter author also reported the occurrence of rheumatic fever in but one of another pair of identical twins and concluded that, while heredity may be of considerable importance in the pathogenesis of rheumatic fever, infection plays an equally important role. In all of these reported cases of rheumatic fever the environments of the twins were also identical. This fact obscures the actual role played by the hereditary factors.

Congenital cardiac defects<sup>4</sup> have also been reported in each of identical twins. Kahler and Weber<sup>5</sup> further observed that the frequency of such defects in identical twins was twice that found in nonidentical twins.

Parade and Lehmann<sup>6</sup> reported the occurrence of angina pectoris in identical twins. These twins died within a year of each other, both had a thrombosis of the descending branch of the left coronary artery and a myocardial infarct in the same region of the heart. The environments of these two men were not similar.

Essential hypertension also has been reported<sup>7</sup> in identical twins with similar environment.

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From the Harold Brunn Institute for Cardiovascular Research and the Department of Psychiatry, Mount Zion Hospital.

1 Wise, H. B., Comeau, W. J., and White, P. D. An Electrocardiographic Study of Twins, *Am Heart J* **17** 201, 1939.

2 Morgan, J. E., and Webster, S. J. Rheumatic Fever Followed by Mitral Heart Disease in Each of Identical Twins, *J A M A* **110** 1744 (May 21) 1938.

3 Perry, C. B. Rheumatic Heart Disease in Identical Twins, *Arch Dis Childhood* **15** 177 (Sept) 1940.

4 Giustra, F. X., and Tosti, V. G. True Cor Biloculare in Identical Twins, *Am Heart J* **17** 249, 1939.

5 Kahler, O. H., and Weber, R. Zur Erbpathologie von Herz- und Kreislaufkrankungen, *Ztschr f klin Med* **137** 507, 1940.

6 Parade, G. W., and Lehmann, W. Angina pectoris bei erbgleichen Zwillingen, *Klin Wchnschr* **17** 1036, 1938.

7 Frohlich, K. Jugendliche Zwillinge mit arteriellen Hochdruck, *Med Klin* **33** 1196, 1937.

In the present communication we are reporting the results of a study of identical twins in only one of whom hypertension and coronary disease were present. Each twin was subjected to a routine physical examination, a psychologic assay, an electrocardiographic study and determination of the renal blood flow and of the glomerular filtration rate.

#### UNIOVULAR ORIGIN OF THE TWINS ILLUSTRATED BY REPORTED ON

Although the only incontrovertible proof of the uniovular origin of twins is the finding of a single placenta at the time of their delivery, Newman<sup>8</sup> listed other criteria which in his opinion establish the identity of twins. The birth records of our twins are not available, since the physician who delivered them is dead and the records were lost. We thus do not know if there was one placenta. Newman's criteria were met by our set of twins for they had (a) identical color, texture and form of hair, (b) striking similarity in general appearance (fig. 1), (c) identical color and color pattern of the iris, (d) identical color and texture of skin, (e) identical eyelashes, eyebrows, lips, shape of ears and teeth, (f) identical hands, fingers and finger nails, (g) identical general character patterns and main lines of finger and palm prints, and (h) blood of the same type.

The evidence of blood type is of especial importance in these twins. A serologic study was done by Dr. Charles Weiss, director of clinical laboratories, Mount Zion Hospital, San Francisco, and Dr. Phillip Levine, bacteriologist of Beth Israel Hospital, Newark, N. J., who have done special work in this field. The blood of both the twins was of the following type: A, M+, N+, Rh—, H<sub>1</sub>+. Such an agreement in blood type is an almost incontrovertible proof of the identity of the twins. Although such similarity in the blood of two persons is possible statistically, practically it is impossible to find it unless they are identical twins. One must remember that even identical twins show a certain amount of variation. This was true in our twins. The healthy twin was always more robust physically, and when both grew up the healthy twin weighed 30 to 50 pounds (13 to 23 Kg.) more than the patient. Intellectually, the healthy twin was also more alert and was slightly ahead of the patient in school.

#### CASE STUDY OF THE PATIENT AND OF HIS BROTHER

*Clinical Study*—The patient, G. G., was a man aged 54 at the time we saw him. In 1931 he was found to have hypertension. However, at this time he experienced no symptoms. In 1937 a routine electrocardiogram was taken, apparently because of his persisting hypertension. It was not until 1939, however, that he began to have attacks of severe substernal pain radiating down his left arm. These attacks were particularly likely to occur after strenuous exertion, excitement or ingestion of a heavy meal. Usually they subsided within several minutes if nitroglycerin was given. The frequency and severity of his attacks increased until he was forced to quit work at the end of 1940. When seen by us in February 1941, he had daily attacks of anginal pain. There was no familial history of hypertension. The patient had never been exposed to toxic quantities of lead and had never used tobacco in any form. He had lived in San Francisco from birth.

On physical examination the patient was observed to be a robust, vigorous person, in no obvious distress or pain. Examination of his eyes revealed a moderate tortuosity of his retinal arteries, with marked auriculoventricular depression. No hemorrhagic or exudative areas were seen in the retina of either eye. Examination of the heart revealed no murmurs, but numerous extrasystoles were heard, apparently ventricular in origin. Fluoroscopic examination showed a moderate dilatation of the ascending aorta and slight enlargement of the left ventricle. The radial arteries felt thickened. The blood pressure (right brachial artery) was 180 systolic and 110 diastolic. There were no peripheral signs of cardiac decompensation.

8 Newman, H. H. *Multiple Human Births*, New York, Doubleday, Doran & Company, Inc., 1940.

Intravenous pyelography showed no gross abnormality of the kidneys. Microscopic and chemical examination of the urine likewise failed to reveal any abnormality.

R. G., the twin brother of the patient, had never had any signs or symptoms suggestive of cardiovascular disease. He submitted to the diagnostic procedures herein reported because he wished to aid in this study. He also had never used tobacco in any form.

On physical examination the patient was observed to be a calm, apparently healthy person. Examination of his eyes revealed no abnormalities either of the retina or of the retinal vessels. Examination of the heart showed no abnormality in size, rhythm or dynamics. The radial arteries were not palpably thickened. The blood pressure (right brachial artery) was 135 systolic and 80 diastolic.

Microscopic and chemical examination of the urine gave negative results.

*Personality Study*—The patient, a large, stocky middle-aged man, aged 54, was eager to have the examination completed as soon as possible so that he could start on his vacation. He was tense, somewhat restless and always in a hurry. He gave a history of his illness along the lines already reported.

The patient came from sturdy Irish-German stock. His mother was living and well at 77 years of age, a tense, nervous woman. The patient's father died at the age of 65, from pernicious anemia.

The patient stated that he was a twin, being thirty-five minutes older than his brother. He described his brother as being somewhat taller than he and always weighing about 50 pounds more than he. As infants they could not be told apart and had to have blue and



Fig. 1—The twins at the age of 3 years

pink ribbons to identify them. The brother was a better scholar, but the patient was a better mixer. From early adolescence the patient had joined all kinds of organizations, currently he was a Woodsman, a thirty-fifth degree Scottish Rite Mason, a member of a band and a participant in other activities.

As a child, the patient was very active, and at the age of 11 years he began to work in an engraving shop. At the same time he continued in an evening grammar school. He was able to complete an evening high school course. At the age of 18, the patient entered the United States postal service, where he made a good record. It was his job, finally, to teach the younger postal clerks how to work more efficiently, and he was made a "speed-up man," that is, he was to set the pace for the slower men to follow. The patient made such an excellent record in the postoffice that one of the larger banks employed him to take charge of their mail department. Soon afterward he was put in charge of the young men who were in training at the bank. Irrespective of previous education, the young men who expected to make a career in the bank had to start in the patient's department as messengers and junior clerks. He built crews of men, one after another, from which the stable organization of the bank was supplied. He took responsibility for their later performances.

As to personality, the patient was dynamic, eager, quick, excitable, anything he did, he "jumped" to do. It was this quality that made him known as a "builder of men" and as an example for young men to follow. His wife described him as a man of a worrisome nature, he never let a bill go and everything had to move ahead of schedule. He constantly worried about whether his work was done well and at night thought about his work and went over details again and again. He was very friendly and had no enemies. He continually did favors for other people. The patient described himself as "too damned conscientious" and "too serious." There was a certain strain about him, and he always seemed to be too busy to do

things easily. The patient described himself as being very sensitive, never letting anybody know how he felt, never, never letting himself go and always concealing his emotions. To his wife he was a "high pressure" man who rarely lost his temper. She did not feel that he was very sensitive, but she felt herself to be sensitive, because of crying easily. She stated that he never showed how he really felt and that whatever he wanted to do he did in a hurry, "skipping and jumping" all the time. His wife said, further, that he always slept poorly and got up at 5 a. m., although there was no need for it, and as he got older he seemed to be more and more on the go. Sexually, the patient was described as an "overly passionate man." The patient had one child, a woman of 31 who was married and happy.

The patient's brother, R. G., looked strikingly like the patient. He had the same build and the same facial expression, especially, their voices were strikingly alike. R. G. repeated stories of how alike they were as children and gave numerous incidents of how they were confused. They could not be told apart at school. The patient seemed to R. G. more of a nervous type, whereas R. G. himself was steadier and more easy going. R. G. said G. G. was a restless person who could not sit still. The patient had several changes of jobs, always being more ambitious and eager than the brother.

### *Similar and Contrasting Characteristics*

(In the patients' own words)

<i>Patient</i>	<i>Brother</i>
Nickname "Speed-up George"	Nickname "Lead-in-the-pants"
Nervous type	Not so nervous
Fast worker	Also fast, but not so fast
Always on the go, flies to things	Excited occasionally, but not so excitable
Always "bing-bing"	
Played tackle in high school (145 pounds [65 Kg])	Played center in high school (165 pounds [74 Kg])
Usual weight, 175 pounds (79 Kg)	Usual weight, 225-250 pounds (101 to 112 Kg)
He was the wilder of the two, always feeling more devilish	More steady, a little smarter, graduated ahead of the patient
	Was considered pretuberculous and was out of school for two years as an adolescent, in spite of this graduated ahead of the patient
More active socially, more with people, does favors for people	More selfish, more to himself, less interested in people
Better mixer	More satisfied to be at home
Few temper tantrums, holds resentments, carries hostility a long time, does not show it	People say he is quick tempered, lets his temper out, gets over hurts quickly
Changed jobs several times	Stayed in one job 33 years
Always close mouthed	Always close mouthed
Very active in sports	Very active in sports
Cares more for clothes, more wiry	Cares less for clothes, more husky
Occasional drinking	Occasional drinking

In summary, the patient was by far the more dynamic of the two, more aggressive, more energetic, more active, probably more successful, although in the past few years this had been canceled by the fact that the patient had been ill. Both had a certain amount of financial security, but the patient was worried about his future, although he had savings and his wife was working. The brother was a widower, and he continued to work, being in excellent health. The two men cared for each other strongly, although there had been some estrangement at different periods in their life, due to the fact that their wives did not like each other.

In spite of the fact that the patient and his brother were strikingly alike, undoubtedly there was a certain feeling of inferiority on the part of the patient because his twin was somewhat stronger physically and more alert intellectually. The patient's brother had to stay out of school for two years on account of a suspicion of tuberculosis, yet he graduated from grammar school ahead of the patient. It is quite possible that it was this feeling of comparative inadequacy that made the patient anxious to prove that he was as good as or better than his

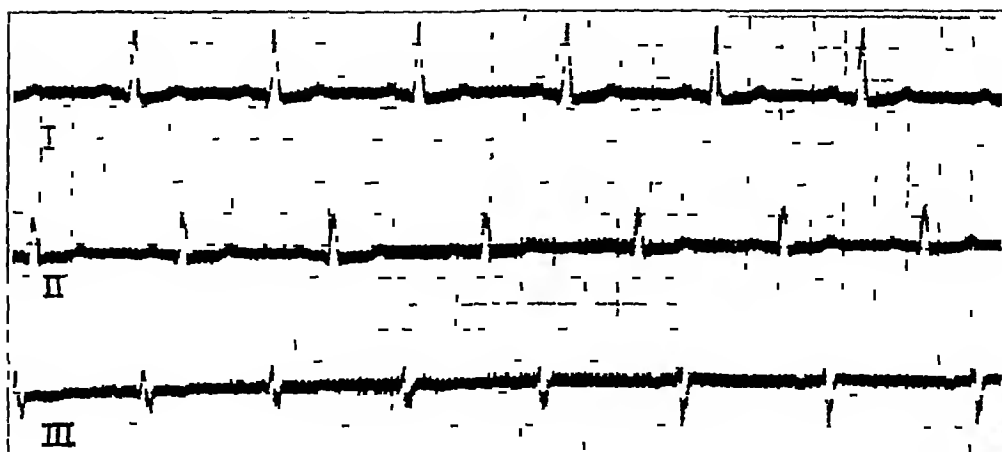


Fig 2—Electrocardiogram of G G taken in 1937, before the onset of the attacks of angina pectoris

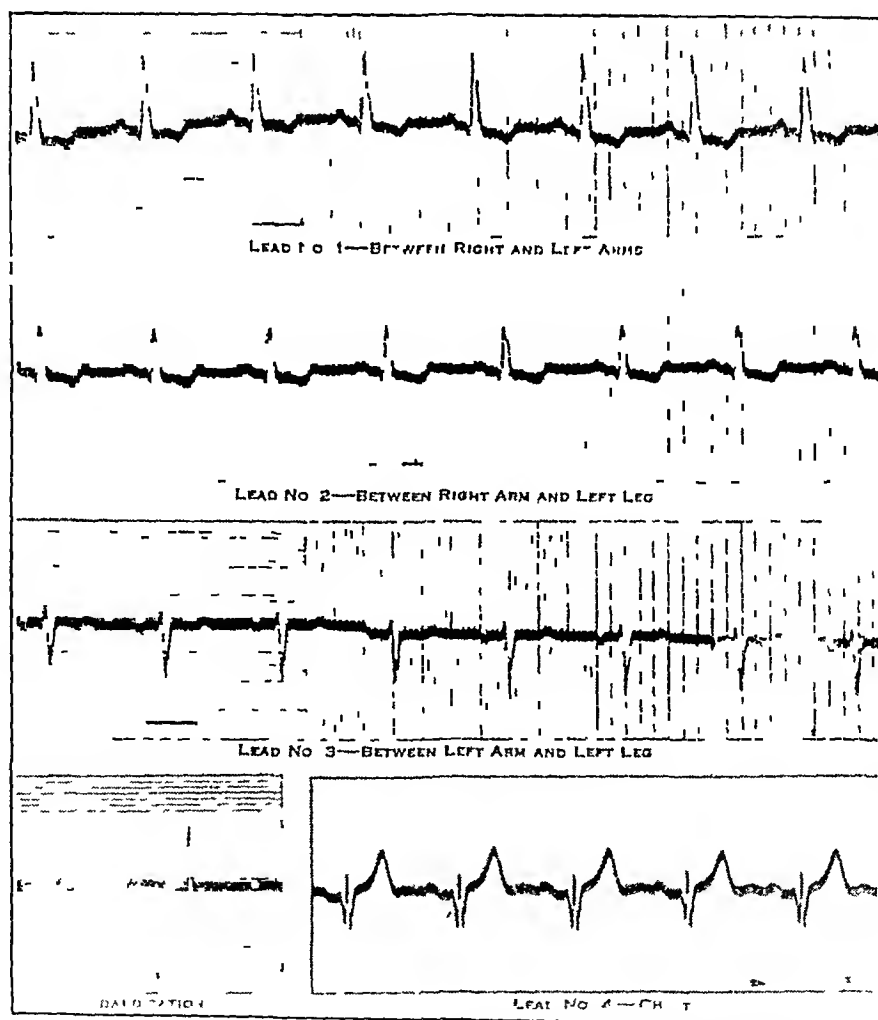


Fig 3—Electrocardiogram of G G taken in 1940, approximately one year after the onset of the attacks of angina pectoris

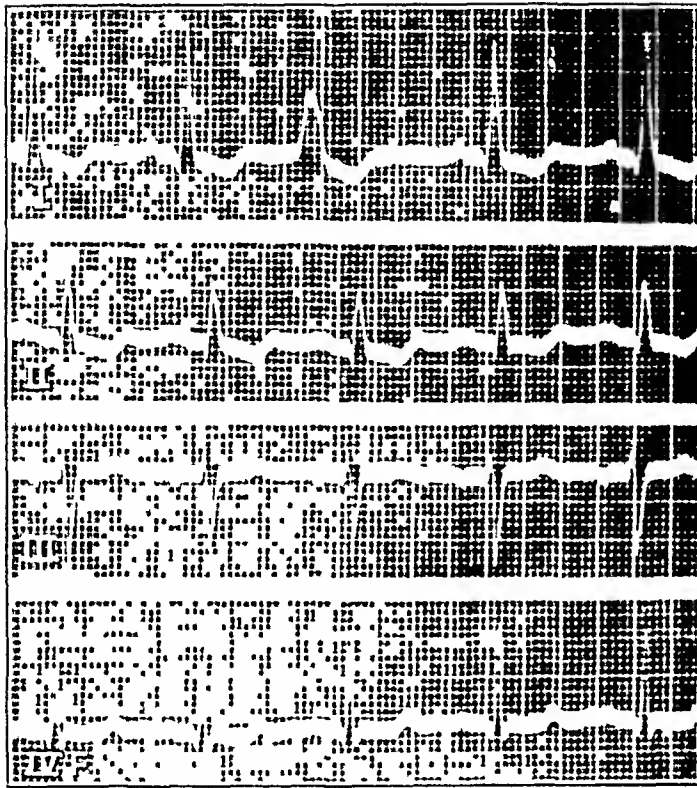


Fig 4—Electrocardiogram of G. G. taken on Dec. 20, 1941

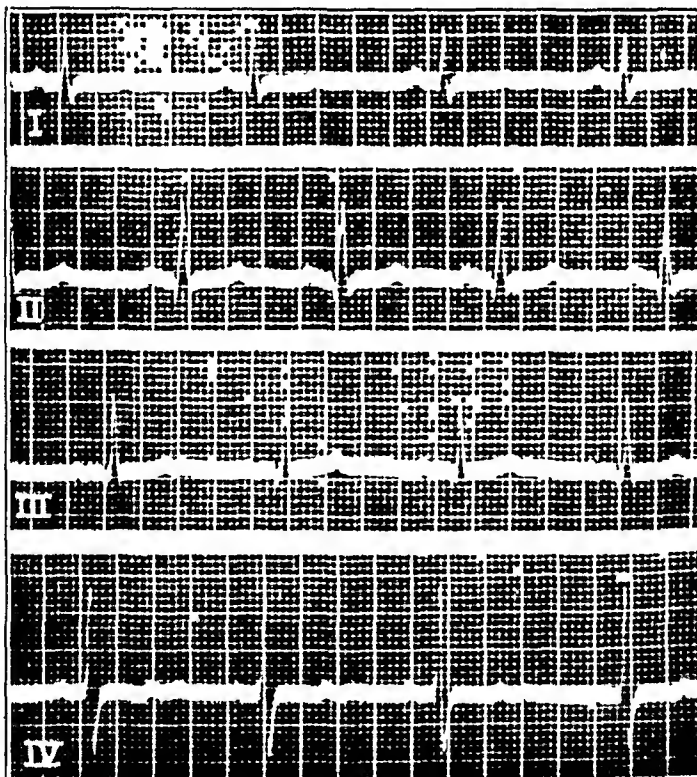


Fig 5—Electrocardiogram of R. G., the patient's normal brother, taken on Dec. 20, 1941

brother and made him change jobs, take different positions and take on work entailing more responsibility and greater compensation. The most important primary difference, however, lies in the fact that the patient had always been a person who tried to please everybody and was always at every one's beck and call, never letting himself go, always suppressing his feelings, especially his hostile feelings. Franz Alexander, of Chicago, and his associates<sup>9</sup> have expressed strongly the belief that hostility is an important psychologic factor in the causation of hypertension. No psychologic tests were given, for with persons of this age and with their cumulative experiences such tests would not be indicative of any true difference of intelligence.

*Renal Blood Flow and Inulin Clearance*—The diodrast and the inulin clearance method<sup>10</sup> were employed for determination of the renal blood flow and of the glomerular filtration rate respectively. The procedure followed was identical with that previously reported by one of us.<sup>11</sup>

It was found that the patient had a total effective renal blood flow of 606 cc per minute. His twin brother was found to have a total effective renal blood flow of 725 cc per minute. Both of these flows are low as compared with the average value, of 1,280 cc per minute.<sup>11</sup> It should be noted, however, that there is no great difference between the two observed renal blood flows.

The similarity in the inulin clearance of the twins was even more striking, for the clearance of the patient was 97.8 cc per minute, that of his brother was 96 cc. The filtration fraction was 21.5 per cent for the patient and 24.0 per cent for the normal twin.

*Electrocardiographic Study*—The patient's first electrocardiogram (fig 2), taken on March 4, 1937, revealed no particular abnormalities other than a low T wave in leads I and II, and complete absence of the T wave in lead III and a left axis deviation. However, the second electrocardiogram (fig 3), taken on Aug 29, 1940, showed unmistakable evidence of myocardial damage, strongly suggestive of disease of the coronary arteries: (1) depression of the ST segment in leads I and II, (2) inversion of the T wave in leads I and II and (3) slurring of the QRS complexes in all leads. The last electrocardiogram (fig 4) was taken on Dec 20, 1941 and except for the presence of an occasional ventricular extrasystole was essentially similar to the immediately preceding electrocardiogram.

The electrocardiogram of the patient's brother (fig 5), taken on Dec 20, 1941 on the other hand, appeared essentially normal.

#### COMMENT

Most recent articles concerned with renal blood flow in hypertensive persons<sup>12</sup> suggest the possibility that renal ischemia is not the causative agent in the pathogenesis of clinical hypertension. There is also evidence<sup>13</sup> that renal ischemia is not the causative agent in the pathogenesis of experimental renal hypertension.

9 Anderson, O. D., Paolmonter, A., and Liddell, H. S. Some Cardiovascular Manifestations of the Experimental Neurosis in Sheep, *Psychosom Med* **1** 93, 1939. Katz, L. N., and Leiter, L. Present Conception of "Essential" Hypertension, *ibid* **1** 101, 1939. Solomon, A. P., Darrow, C. W., and Blaurock, M. Blood Pressure and Palmar Sweat (Galvanic) Responses of Psychotic Patients Before and After Insulin and Metrazol Therapy, *ibid* **1** 118, 1939. Alexander, F. Psychoanalytic Study of a Case of Essential Hypertension, *ibid* **1** 139, 1939. Saul, L. J. Hostility in Cases of Essential Hypertension, *ibid* **1** 153, 1939. Miller, M. L. Blood Pressure Findings in Relation to Inhibited Aggressions in Psychotics, *ibid* **1** 162, 1939. Alexander, F. Emotional Factors in Essential Hypertension, *ibid* **1** 173, 1939.

10 Smith, H. W., Goldring, W., Chasis, H., and Ranges, H. A. Observations on the Effective Renal Blood Flow and Functional Excretory Mass in Man with Especial Reference to Essential Hypertension, *Am J Physiol* **123** 189, 1938.

11 Friedman, M., Selzer, A., and Rosenblum, H. The Renal Blood Flow in Hypertension, *J A M A* **117** 92 (July 12) 1941.

12 Chesley, L. C., and Chesley, E. R. Renal Blood Flow in Hypertensive Women, *J Clin Investigation* **19** 475, 1940. Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W. Effective Renal Blood Flow in Subjects with Hypertension, *ibid* **20** 637, 1941. Friedman, M., Selzer, and Rosenblum.<sup>11</sup>

13 Corcoran, A. C., and Page, I. H. Renal Blood Flow in Experimental Hypertension Due to Constriction of the Renal Artery, *Am J Physiol* **133** 248, 1941. Friedman, M., Sugarman, H., and Selzer, A. The Relationship of Renal Blood Pressure and Blood Flow to the Production of Experimental Hypertension, *ibid* **134** 493, 1941.



The finding of renal ischemia of approximately the same degree in identical male twins with hypertension present in only one of them further suggests the probability that renal ischemia is an incidental factor, not a causative one, in the pathogenesis of clinical hypertension, otherwise both twins would have been hypertensive.

The clearcut demonstration of electrocardiographic and clinical signs of coronary artery disease in one of a pair of identical twins does not exclude the possibility of coronary artery disease in the apparently well twin brother. For both may have had a basic involvement of the coronary vasculature, but the fortuitous occurrence of thrombosis in but one of the twins may have given rise to the signs and symptoms observed in the patient.

It is possible too, that the long-standing hypertension in the patient may have led to advanced degeneration of the coronary arteries. Certainly, the facts available are not sufficient to permit a certain conclusion as to the degree of underlying sclerosis of the coronary arteries in each of the twins.

A description of the contrasting personalities of these identical male twins has been included in this report because, other than the cardiovascular differences noted, they composed the only striking difference observed. Whether the lifelong existence of extreme tension and drive in the patient bore a causal relation to his hypertension is, of course the problem. Certainly the similarity in the heredity and early environment of these identical twins stresses the divergency in personality drives as a possible cause of the hypertension found in one of them.

#### CONCLUSIONS

Only one of a pair of identical twins had hypertension and coronary artery disease.

Determinations of renal blood flow and of glomerular filtration were performed on both the normotensive and the hypertensive twin. The renal blood flow was found to be similarly reduced in both twins. The glomerular filtration rates also were similar.

Electrocardiograms of the patient showed evidence of myocardial damage, while a tracing made for his brother was normal.

The evidence suggests that psychologic factors may have been of primary significance in the production of hypertension in the affected twin.

Dr Tom Addis, of Stanford University, looked over the manuscript.

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# MYOCARDITIS IN BRONCHIECTASIS

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Inflammatory disease of the lung is not commonly associated with myocarditis. White<sup>1</sup> remarked that pneumonia, either lobar or bronchial, may prove a great strain on an already weakened or diseased heart but that it does not itself cause serious heart disease except in rare circumstances. In a general study of 240 cases<sup>2</sup> of myocarditis the disease was found to be associated with lobar pneumonia 7 times and with bronchopneumonia 19 times. If one considers the frequency of pneumonia, these figures are not high. However, in pursuing the study of myocarditis it was noted that myocarditis was associated relatively more frequently with bronchiectasis than with uncomplicated pneumonia. This was the more noteworthy since the relevant literature barely mentions myocarditis in relation to bronchiectasis. Because myocarditis associated with bronchiectasis has been given little attention, it was considered of interest to bring forward certain facts gleaned from a study of the heart in a number of cases of bronchiectasis, in the hope that from a study of the clinical records and anatomic changes of the heart some data might be elicited concerning myocarditis, which, in general, is a rarely observed clinical entity uncommonly confirmed at postmortem examination.

As mentioned before, there are few references available on this subject. Occasional statements, however, are found ascribing death to heart failure. Jex-Blake<sup>3</sup> merely mentioned that 3 of 110 patients with bronchiectasis died of heart failure. Moll<sup>4</sup> referred to 4 patients out of 55 who died as a result of heart failure. Neither author gave any details as to the type of heart disease responsible for the 7 deaths. Ogilvie,<sup>5</sup> more recently, stated that myocardial damage occurs as a late result of chronic sepsis but is infrequently the direct cause of death. Wiese,<sup>6</sup> in a review of bronchiectasis, made no mention of heart disease as a complication. Merklen<sup>7</sup> observed a patient with long-standing bronchiectasis and rheumatic heart disease in whom a subacute bacterial endocarditis eventually developed.

Among 6,257 patients who came to autopsy, 152 were found to have bronchiectasis, and in 8 there was associated myocarditis. Among the 152 patients with bronchiectasis, there were 14 less than 8 months old. One of these children had myocarditis. In the following concise abstract clinical data pertinent only to the cardiovascular apparatus of the 8 patients with myocarditis are given.

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Aided by a grant from the Otto Baer Fund

From the Department of Pathology, Michael Reese Hospital. The department is in part supported by the Michael Reese Research Foundation.

1 White, P. D. *Heart Diseases*, ed. 2, New York, The Macmillan Company, 1937.

2 Saphir, O. Myocarditis. A General Review, with an Analysis of Two Hundred and Forty Cases, *Arch Path* **32** 1000 (Dec.) 1941, **33** 88 (Jan.) 1942.

3 Jex-Blake, A. J. A Lecture on Bronchiectasis, *Brit M J* **1** 591, 1920.

4 Moll, H. H. A Clinical and Pathological Study of Bronchiectasis, *Quart J Med* **1** 457, 1932.

5 Ogilvie, A. G. The Natural History of Bronchiectasis, *Arch Int Med* **68** 395 (Sept.) 1941.

6 Wiese, O. Die Bronchiektasenkrankheit, *Zentralbl f d ges Tuberk-Forsch* **46** 113, 1937.

7 Merklen, P. Dilatazione bronchiale e insufficienza mitralica, *Gazz d osp* **54** 200, 1933.

## CLINICAL DATA

The ages of these patients were 5 weeks and 33, 42, 47, 48, 55, 67 and 77 years respectively. There were 3 females and 5 males. The 5 week old infant (case 1) had congenital bronchiectasis, and collapse occurred when a thoracentesis was performed. The temperature ranged from 98 to 104 F. The 33 year old man (case 2) had had symptoms of bronchiectasis for a number of years and entered the hospital because of headaches and weakness. There was gradual development of signs of meningitis, which was thought to be the result of a cerebral abscess secondary to the bronchiectasis. Several days before he died cyanosis and tachycardia were noted. The heart was not enlarged, and the rhythm was normal. The pulse rate varied from 100 to 124, the temperature varied from 99 to 103 F, the arterial blood pressure was 160 systolic and 105 diastolic. The 42 year old woman (case 3) had an old history of tuberculosis of the lungs with resulting bronchiectasis. Toward the end of her stay in the hospital cyanosis and dyspnea developed. Her temperature was always about 100 F, the pulse rate 105, and the arterial blood pressure 106 systolic and 64 diastolic. Clinically the heart was enlarged. The disease of the 47 year old woman (case 4) was diagnosed as bronchiogenic carcinoma. While in the hospital she became dyspneic and cyanotic and tachycardia developed. The heart was enlarged, and a soft apical systolic murmur was heard. At that time the pulse rate was 136 per minute, while the temperature was 99 F. Before death the pulse became irregular. This was the only patient in the series for whom a diagnosis of myocarditis was made. The 48 year old man (case 5), who gave a history of old bronchiectasis, began to have headaches after an apparently insignificant trauma. After a few fainting spells, he died rather suddenly. Because of the trauma and sudden death, the case was referred to the coroner. At autopsy meningitis was found, in addition to the old bronchiectasis and the acute myocarditis. The 55 year old man (case 6) gave a history of old, unresolved pneumonia, nineteen years before. On examination he was cyanotic and had edema of both lower extremities. The heart was enlarged and the heart sounds were distant. The temperature was 99 F, the pulse rate 104 per minute and the arterial blood pressure 100 systolic and 70 diastolic. For the 67 year old man (case 7) a clinical diagnosis of bronchiectasis associated with coronary arteriosclerosis (thrombosis?) and a myocardial infarct was made. The diagnosis was confirmed at autopsy. The heart rate was rapid and the rhythm regular. The temperature was around 101 F, the pulse rate varied but usually was 128 per minute, and the arterial blood pressure varied from 142 systolic and 76 diastolic to 110 systolic and 74 diastolic. There were three electrocardiograms. The first only is shown here (fig 1). The heart rate was 107. The P-R interval was 0.18 second. The QRS complex was upright in the limb leads, and small in lead III with a Q wave present. There was an S wave present in lead I. The P wave in lead I was relatively small, and the P waves in leads II and III were tall and peaked. The ST segments in leads I and II were isoelectric. The ST segment in lead III was slightly elevated. The T waves in leads I and III were small and the T wave was upright in the limb leads. The QRS complex in lead  $CF_2$  was almost entirely down, and the T waves in leads  $CF_2$  and  $CF_1$  were inverted. The interpretation by Dr. L. N. Katz was as follows: There was sinus tachycardia. This is a definitely abnormal record. The P waves suggest P-pulmonale. The QRS complex in lead  $CF_2$ , the Q wave in lead III and the inversion of T in the chest leads suggest an atypical coronary pattern resembling anterior wall infarction. It was decided after the record was made that another should be taken in forty-eight hours.

to rule out a recent myocardial infarction (In lead  $CF_4$  an auricular premature systole was found, this is not shown in the illustration)

Another record was made in forty-eight hours and still another in another forty-eight hours. They revealed some evolution, chiefly in the chest leads. This consisted of T becoming upright in these leads. At the same time a persistent auricular flutter with irregular conduction varying from 2:1 to 3:1 was present, and in the later record this was replaced by a regular 2:1 conduction. The evolution in these three records was not typical of a recent myocardial infarction, and the diagnosis was therefore entertained of an old myocardial infarction of the anterior wall with chronic coronary insufficiency and a temporary exacerbation at the time of the record shown in the illustration.

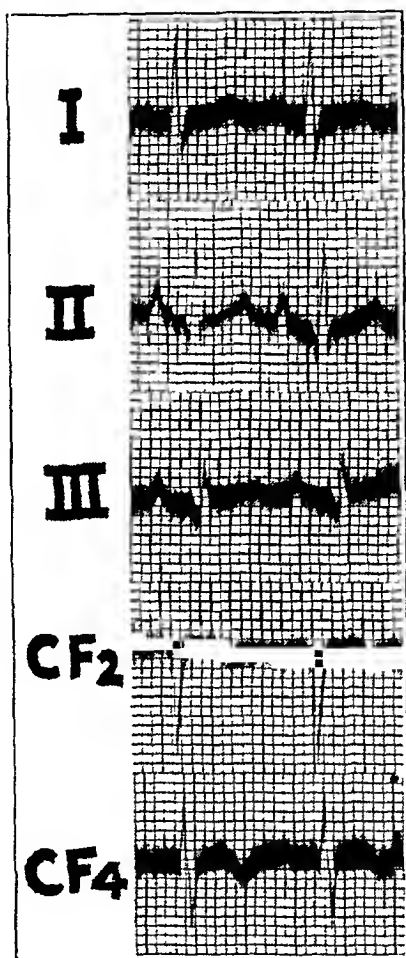


Fig 1 — First electrocardiogram taken in case 7

The 77 year old man (case 8) had diabetic gangrene of a lower extremity, for which the leg was amputated. The heart was enlarged, and the heart tones were fairly clear. The temperature was about 100 F, the pulse rate 128 per minute and the arterial blood pressure 170 systolic and 105 diastolic. He died rather unexpectedly following the amputation.

#### AUTOPSY DATA

At autopsy bronchiectasis was found in every instance. The lungs of the 5 week old infant (case 1) gave evidence of the congenital form of bronchiectasis. The 47 year old woman (case 4) had bronchiogenic carcinoma with bronchiectasis in other portions of the lung, and the 42 year old woman (case 3) had severe ulcerating tuberculosis of the lung with much fibrosis and involvement of the bronchi and

diffuse bronchiectasis. The remainder of the patients showed evidence of old or recent inflammatory disease in the lung in addition to the bronchiectasis.

The heart was enlarged in all patients with the exception of the infant and the patient who had the bronchiogenic carcinoma (case 4), the heart of the latter weighed 265 Gm. In the remainder of the 8 patients, the hypertrophy was more prominent in the right ventricle. The heart of the patient whose disease was diagnosed clinically as myocardial infarction revealed an old aneurysm of the left ventricle, involving the apex and the adjacent interventricular septum. Frank areas

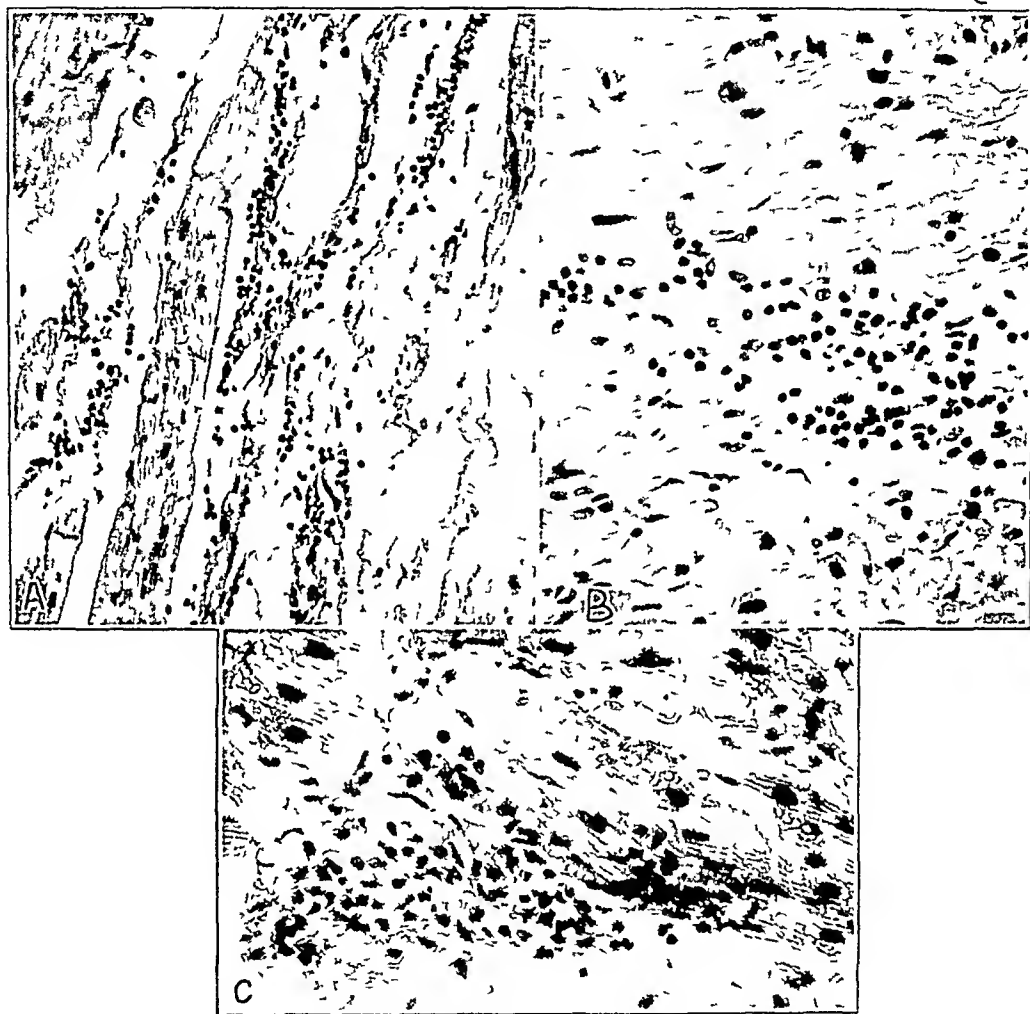


Fig 2—Myocarditis. *A* shows the presence of lymphocytes and a few polymorphonuclear leukocytes in the interstitial tissue (iron-hematoxylin-eosin preparation,  $\times 120$ ), *B*, lymphocytes and old connective tissue in the interstitial tissue space (hematoxylin-eosin preparation,  $\times 260$ ), *C*, lymphocytes and an occasional polymorphonuclear leukocyte in part in the interstitial tissue and in part replacing heart muscle fibers (iron-hematoxylin-eosin preparation,  $\times 280$ ).

of fibrosis undoubtedly the result of coronary arteriosclerosis were found in 2 additional instances.

Grossly, myocarditis was not recognized in a single instance, though a diagnosis of cloudy swelling of the myocardium was made on all the hearts. On histologic examination, however, the existence of myocarditis was obvious.

On microscopic examination in case 1 many neutrophilic polymorphonuclear leukocytes were seen extending through the entire wall of the myocardium but particularly pronounced in the right ventricle. There was also an acute pericarditis.

In case 2 the inflammatory cells consisted principally of mononuclear cells, particularly pronounced in the perivascular spaces. An occasional polymorphonuclear leukocyte and a few fibroblastic cells were also noted. In case 3 a distinctly edematous material was found in the interstitial tissue, and many polymorphonuclear leukocytes and lymphocytes were noted. No tubercles were recognized, nor did the Ziehl-Neelsen stain reveal any acid-fast bacilli. In case 4 the myocardium showed an increase in connective tissue throughout, and between the interstitial tissue fibers lymphocytes and endothelial leukocytes were noted. The vessels on section showed no change. The myocardial changes were interpreted as true chronic myocarditis. In case 5 there were disclosed a number of neutrophilic polymorphonuclear leukocytes, mononuclear cells and occasional plasma cells. These cells were found in the interstitial tissue but also could be made out replacing some heart muscle fibers. Bacterial stains showed the presence of intracellular and extracellular gram-positive cocci. The heart of patient 6, who was classified clinically as dying from myocardial failure, showed a new formation of connective tissue situated diffusely between the muscle fibers, and lymphocytes, endothelial leukocytes and a few plasma cells were found distributed throughout the newly formed connective tissue. The coronary arteries showed no sclerotic lesion. These changes were interpreted as chronic myocarditis. In case 7 sections of the myocardium showed an old myocardial infarction which was found on gross examination. Other areas of fibrosis were also noted. However, in a number of other sections neutrophilic polymorphonuclear leukocytes, lymphocytes and large mononuclear cells were seen distributed throughout the interstitial tissue. There was no evidence of recent infarction in these regions. In case 8 old connective tissue fibers were seen, partially replacing muscle fibers and partially situated in perivascular spaces. Because of the moderate coronary arteriosclerosis, these changes were interpreted as being the result of a vascular disturbance. However, in addition, a number of foci of polymorphonuclear leukocytic infiltration were noted in perivascular spaces and extending along the interstitial tissue. An occasional lymphocyte and a few plasma cells were also seen. Thus, in addition to the fibrosis of the myocardium, a recent myocarditis was encountered.

In summary, a recent myocarditis was encountered in 3 cases (cases 1, 3 and 5). Complicated with myocardial fibrosis because of coronary arteriosclerosis, recent myocarditis was found in 1 instance (case 8) and coincidental with an aneurysm of the heart in another instance (case 7). Subacute myocarditis was encountered once (case 2) and true chronic myocarditis twice (cases 4 and 6).

#### COMMENT

It is noteworthy that clinically the diagnosis of myocarditis was made in only a single instance (case 4). The diagnosis was arrived at because of the enlarged heart and the high pulse rate, which eventually became irregular in the face of the only slightly elevated temperature (99 F). In retrospect, such a discrepancy between pulse rate and temperature was definitely noted in 3 patients. There were 2 other patients who perhaps had a slight discrepancy between temperature and pulse rate which may be significant in this respect (case 6, temperature 99 F, pulse rate 112, case 7, temperature 101 F, pulse rate 128). One of these patients (case 6), the 55 year old man, was considered clinically to have died of heart failure. The heart was enlarged, the heart sounds were distant, and there were edema of the lower extremities and cyanosis. The heart at autopsy showed minimal coronary arteriosclerosis, but marked myocardial fibrosis with a number of inflammatory cells was still clearly recognizable. This was 1 of the 2 instances in which a diagnosis of true chronic myocarditis was made. There was nothing else found in

the records of all these patients that could be construed as evidence in favor of the diagnosis of myocarditis. It must of course be realized that these data were taken from the records of the relevant patients and that these patients were not examined with a view to either ruling out or confirming myocarditis.

Three of the 8 patients died unexpectedly. Sudden death of patients with myocarditis is often stressed.<sup>2</sup> Reference will be made here only to the report of Lisa,<sup>8</sup> who reviewed the autopsies on 41 patients who died suddenly. In 36 of these there was acute myocarditis.

Histologically the myocardial lesions were not characteristic in any respect. The inflammatory cells were found in the interstitial tissue but also replaced occasional muscle fibers. The involvement of the interstitial tissue, however, was more pronounced. Though neutrophilic polymorphonuclear leukocytes predominated in the cases of more recent involvement, other types of inflammatory cells were noted. A predominance of eosinophilic cells was not present. In the hearts considered as showing true chronic myocarditis, there was much newly formed connective tissue, with a majority of lymphocytic cells. The Wassermann reactions of the patients were negative, and nothing was found at autopsy from which a diagnosis of syphilis could possibly be inferred.

The cause of the myocarditis in some of these instances, in which there were no other infections, was very likely the bronchiectasis. The suppuration, the large number of bacteria present in the dilated bronchi and the acute and chronic inflammation of the wall of the bronchi can easily constitute the primary focus to which the myocarditis may be ascribed. Yet in only 1 instance were bacteria found in the myocardium (case 5). In not a single instance was there an endocarditis. The chronicity of the bronchiectatic lesion may account for the subacute and chronic myocarditis in some of the cases. In a previous study<sup>7</sup> it was pointed out that there is little concrete evidence for the assumption that tonsillar infection may give rise to myocarditis. However, it seemed evident that more severe infections of the upper respiratory tract may occasionally cause myocarditis in the absence of endocarditis. From this study bronchiectasis and the concomitant inflammatory changes must be considered among the causes of myocarditis. It must be emphasized that it cannot be decided whether the myocarditis found in the patients with meningitis, abscess of the brain and gangrene was coincident with these lesions and possibly a manifestation of sepsis or was the direct result of the bronchiectasis.

Since, as already stated, there are very few references to myocarditis in instances of bronchiectasis, it was considered to be of interest to search for such myocardial complications in related diseases. Thus, reports of autopsies on patients dying of bronchial asthma with bronchitis were studied in this respect. It was interesting to note that such reports were very rare up to about 1930, there have been quite a few reports since that time. Though a number of authors stressed the sudden death of these patients, little attention is seemingly paid to possible microscopic changes in the myocardium, and death is ascribed to asphyxia. Fowler,<sup>9</sup> in reporting the sudden death of 2 such patients, stated that it is worthy of note that necropsy did not reveal any cardiac lesions which might be held responsible for the fatal outcome. Chafee, Ross and Gunn,<sup>10</sup> very recently, however, described a myocarditis in a patient who died suddenly after an asthmatic attack. There were massive infiltra-

8 Lisa, J. R. Pathologic Findings in the Heart in Sudden Cardiac Deaths, *Ann. Int. Med.* **12** 1968, 1939.

9 Fowler, K. Necropsy Studies on Two Patients Dying in Asthma, *Pennsylvania M. J.* **40** 720, 1937.

10 Chafee, F. H., Ross, J. R., and Gunn, E. M. Eosinophilia in Fatal Asthma. Studies of Bone Marrow and Myocardium, *Ann. Int. Med.* **17** 45, 1942.

tions throughout the myocardium of eosinophilic polymorphonuclear leukocytes, a few lymphocytes and plasma cells. Also encountered were small foci of necrosis. Though myocarditis was not mentioned in a second patient who also died suddenly, the description of the myocardium mentioned an infiltration by inflammatory cells. In the fifth patient, the authors again mentioned an acute nonsuppurative myocarditis.

In the autopsy files of the pathology department of Michael Reese Hospital there are records of 3 fatal cases of bronchial asthma. The routine sections of the myocardium disclosed no inflammatory lesions. Because of the findings of myocarditis in these instances of bronchiectasis, a number of new blocks from the myocardium were cut, stained and examined. In 1 of these 3 instances evidence of myocarditis was found on a restudy of the myocardium. Thus, the question must be raised as to whether or not a careful study of the myocardiums of patients with bronchial asthma may not show myocarditis and whether this may be responsible for the sudden death not rarely encountered in these patients. It is clear that a casual microscopic examination of the myocardium cannot disclose the essential lesions. From this experience, many sections must be cut from the myocardium and the myocardium must be most carefully examined for the specific purpose of either finding or ruling out myocarditis before a negative result can be reported. This study of the myocardium in instances of bronchiectasis and bronchial asthma is significant in this respect.

#### SUMMARY

A type of myocarditis occurs in patients with bronchiectasis. It was found at autopsy 8 times among 152 patients and caused unexpected death 3 times. Clinically myocarditis was diagnosed in only 1 instance. The most significant clinical observation in these patients was a discrepancy between the relatively slight elevation of temperature and the high pulse rate. Bronchiectasis with the incumbent severe inflammatory changes constitutes a primary focus to which myocarditis can be ascribed. Also in some patients with bronchial asthma who die suddenly, myocarditis may be a contributory cause of the sudden death. From this study it is clear that in many instances a correct diagnosis as to the presence or absence of myocarditis can be made only if many sections are cut from the myocardium, and most carefully examined for the specific purpose of either finding or ruling out myocarditis.



# PERNICIOUS ANEMIA IN NEGROES

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CHICAGO

AND

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Pernicious anemia is said to be rare in Negroes. Our review of the last 1,000 consecutive patients with pernicious anemia who entered the Cook County Hospital contradicts this observation. This study covers the period from 1931 to 1942, during which 93 Negroes were found to have pernicious anemia. An analysis of the results of our review constitutes the subject matter of this paper.

## REVIEW OF THE LITERATURE

One hundred and six cases (5 doubtful) of pernicious anemia in Negroes are reported in the literature. All the reports are by American authors and 14 of the cases have been reported from the Cook County Hospital by Carr<sup>1</sup> and by Traut<sup>2</sup>. It is noteworthy in this connection that Carr's report which covered the period from 1912 to 1920, included only 6 cases and Traut's, based on the statistics from 1920 to 1926, only 8. These occurred in a total of 390 cases of pernicious anemia observed during this fourteen year period. Since then, perhaps because of a greater interest in pernicious anemia stimulated by the introduction of liver therapy the diagnosis has been made annually in about three times as many cases. This only partially represents a real increase in the number of cases, since in recent years greater numbers of patients have been admitted to the hospital. Moreover, there is an increase in the life span of patients, and some of them have outlived their first or second relapse by virtue of therapy previously administered elsewhere. Nonetheless, we feel that increased awareness and more frequent recognition are mostly responsible for the threefold increase.

The previously reported cases are summarized in table 1.

Note must be taken of the fact that we deal in this entire series with North American Negroes. Previous writers have almost without exception emphasized the probability of admixture with Caucasian blood. Evans<sup>3</sup> particularly stressed the fact that the 9 patients on whom he reported were all mulattoes. This in no way invalidates our observations, since for practical purposes it is not possible in most instances to ascertain with any degree of certainty the presence or degree of admixture. With few exceptions our patients had the typical dark skin, dark eyes, kinky hair and negroid facies typical of the full-blooded Negro. We fully realize that this in no way excludes even a 50 per cent admixture of white blood. We feel that even if contrary observations were reported from native Negro habitats they would in no way vitiate our findings, since the adaptation of these people to a new mode of living has made them comparable to the Caucasians. Moreover

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From the Department of Medicine, Cook County Hospital

This work was aided by a grant from The Wilson Laboratories, Chicago

1 Carr, J. G. Pernicious Anemia, *Am J M Sc* **160** 737, 1920

2 Traut, E. F. Pernicious Anemia in the Negro, *Illinois M J* **51** 322, 1927

3 Evans, F. A. Pernicious Anemia, Baltimore, Williams & Wilkins Company, 1926, p. 28

from a practical standpoint the question is purely academic, since the North American Negro belongs to a hybrid group. For these reasons we have made no attempt to classify our patients as more or less negroid.

Diagnostic criteria in no way differed from those well established for the disease, i. e., typical hematologic data (macrocytic anemia with high color index and characteristic changes in the red cells, leukopenia, granulocytopenia, and thrombopenia),

TABLE 1—*Summary of Published Reports of Cases of Pernicious Anemia in Negroes*

Author and Reference	Source of Material	Year	Total Admissions	Admissions of Negroes	Total Cases of Pernicious Anemia	Pernicious Anemia in Negroes
Carr <sup>1</sup>	Cook County Hospital, Chicago	1912-1920		"At least 10% of total"	148 (14*)	6
Jamison, S. C. South M J 19 583, 1926	Charity Hospital, New Orleans	1920-1926	122,524	49,188	54	12
Evans <sup>2</sup>	Johns Hopkins Hospital, Baltimore	1889-1922		34,380	578	9 (all mulattoes)
Traut-	Cook County Hospital, Chicago	1920-1926		"33% of total"	256	8
Mathews, H. O. U. S. Vet Bur M Bull 5. 494, 1929	U. S. Veterans Hospital, Tuskegee, Ala.	1923-1928	4,940	4,940	2 (1*)	2 (1*)
Gates, L. R. A Study of Pernicious Anemia, Thesis, University of Michigan Graduate School, 1932, p. 83	University of Michigan and Simpson Memorial Institute, Ann Arbor, Mich.	1925-1932	112,290		580	2
Friedlander, R. D. Am J M Sc 187. 634, 1934	Peter Bent Brigham Hospital, Boston	1913-1932	80,415	4,503	500	3
Strauss, N., and LaPorte, T. F. V. New York State J Med 34 1027, 1934	Morrisania Hospital, Morrisania, N. Y.	1929-1934		8,527	1	1
Kampmeier, R. H., and Cameron, P. B. Am J M Sc 192 751, 1936	Charity Hospital, New Orleans	1926-1936	524,563	247,239	116 (4*)	14 (4*)
Millett, J. Bull. School Med. Univ. Maryland 22 105, 1938	Meadowbrook Hospital, Hempstead, N. Y.	1935-1936			1	1
Granady, J. T. W. J. Nat. M. A. 29 9, 1937	Private cases				4	4
Murphy, W. P. Anemia in Practice, Philadelphia, W. B. Saunders Company, 1939, p. 194	Private cases	1925-1938			578	5
Jones, C. A. Internat. Clin. 3. 258, 1939	Graduate School University of Pennsylvania Philadelphia	1930-1939			34	2†
Harvard Medical School New England J Med 222 734 1940	Peter Bent Brigham Hospital, Boston	1940			1	1
McCraeken, J. B. J. M. A. Georgia 30 49, 1941	Grady Hospital, Atlanta, Ga.	1935-1940		46,006	59	3
Wintrobe, M. M. Clinical Hematology, Philadelphia, Lea & Febiger, 1942, p. 311	Johns Hopkins Hospital, Baltimore	1925-1940		1/2	329	33

\* Doubtful cases

† These two had allergy. There may have been more Negroes.

achylia gastrica, symptoms referable to the anemia and to the gastrointestinal and the nervous system, specific response to the administration of liver extract and in doubtful cases a megaloblastic marrow. It may be stated parenthetically that the blood of Negroes with pernicious anemia shows changes in the red cells much more exaggerated than those seen in Caucasians.

#### ANALYSIS OF CASES (TABLE 2)

*Relative Incidence in White Persons and Negroes*—During the period of the study approximately 800,000 patients were admitted to the hospital, of whom

200,000 were cared for in the medical wards. There were 1,000 patients with pernicious anemia among these, 93 being Negroes, which makes the ratio of white persons to Negroes about 10 : 1. Since white patients outnumbered the Negroes 2 : 1, the corrected ratio would be approximately 5 : 1, or 20 per cent. These figures correspond to an incidence of about 170 cases per hundred thousand among white persons and 36 cases per hundred thousand among Negroes.

Using the figures from table 1 when sufficient information is available we find the following facts:

Of 426,500 white patients, 637 had pernicious anemia—a rate of about 150 per hundred thousand. Of 306,000 Negroes, 31 had pernicious anemia—a rate of about 10 per hundred thousand. The incidence of pernicious anemia in Caucasians seems to be fairly constant, but there is considerable discrepancy between our statistics on Negroes and those of others. In our series the occurrence in Negroes is about three and a half times as frequent as would be expected from previously reported figures.

TABLE 2—Age, Sex and Color Incidence Among One Thousand Patients with Pernicious Anemia\*

Age	Male		Female		Percentage Among the White Persons	Percentage Among the Negroes	Percentage in the Whole Group
	White	Negro	White	Negro			
10-19			2		0.2		0.2
20-29	2	1	6	3	0.0	8.5	1.6
30-39	33	3	30	8	7.0	11.8	7.7
40-49	72	9	69	14	15.6	24.7	16.5
50-59	121	11	130	9	28.1	21.7	27.5
60-69	141	8	119	13	29.1	22.5	28.3
70-79	69	6	82	4	16.8	10.8	16.1
80-89	10		11		2.3		2.1
Totals	452	40	419	53	100.0	100.0	100.0

\* There were 2 Chinese males, aged 55 and 60, 1 Mexican female, aged 31, 17 and 43 and 1 Hindu male, aged 35.

**Male-Female Ratio.**—Of the 93 patients, 40 were males and 53 were females. Since female patients admitted are in a 3 : 5 minority, correcting for this would give an even greater female dominance. During a similar period the ratio in the white population was almost exactly 1 : 1, according to uncorrected data.

**Age Incidence.**—More than two thirds of the patients (64) were between the ages of 40 and 70, without a significant peak in the distribution curve. In this group the percentage distribution was essentially the same as that seen in the general population. At the age extremes, however, two interesting differences were noted. There were many more patients below 40 and far fewer over 70 among Negroes than among Caucasians. The first difference is probably due to the earlier precipitation of the manifestations of pernicious anemia because of the generally poorer diet, while the second could be attributed to a shorter expectancy of life.

SUMMARY AND CONCLUSIONS

Ninety-three cases of pernicious anemia in Negroes were encountered among a total of 1,000 cases of pernicious anemia reviewed.

Pernicious anemia in Negroes occurs at the rate of 36 per hundred thousand hospital admissions, contrasting with the rate of 170 per hundred thousand in Caucasians.

The incidence of pernicious anemia is apparently somewhat higher in Negro females than in males

The age distribution among Negroes is essentially similar to that seen among Caucasians, with two significant differences (a) greater incidence in youth and (b) lower incidence in old age

The pernicious anemia observed in Negroes is identical with that observed in Caucasians

Pernicious anemia in Negroes is more frequent than previous reports would indicate, and its apparent incidence will increase as less and less emphasis comes to be placed on its rarity

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# SPLENOPORTAL VENOUS OBSTRUCTION WITHOUT SPLENOMEGALY

## FURTHER CONTRIBUTION TO THE PATHOGENESIS OF FIBROCONGESTIVE SPLENOMEGALY (BANTI SYNDROME)

PAOLO RAVENNA, M D

CHICAGO

It has been proved beyond a reasonable doubt that the Banti syndrome, a morbid condition characterized by chronic fibrous and congestive splenomegaly, secondary anemia and recurrent hematemeses, may occur independently of any obstruction to the portal circulation<sup>1</sup>. The splenic enlargement thus is not the result of circulatory disturbances in the portal bed, though portal sclerosis and thrombosis may secondarily complicate the picture. A drawback to the general acceptance of this concept lies in the fact that the same clinical and pathologic picture occurs in instances in which the presence of an important obstacle in the portal vessels suggests that the mechanism is passive hyperemia of the spleen. Depending on the nature of the obstruction in individual cases, this condition is termed thrombophlebitic splenomegaly,<sup>2</sup> portal phlebosclerosis<sup>3</sup> or cavernomatous transformation of the portal vein.<sup>4</sup> The current assumption<sup>5</sup> that the splenomegaly is primary in some instances and secondary in others would seem to offer a compromise which is not too convincing. On the other hand, the assumption that all these splenomegalies are secondary, even in the absence of an obstruction, is not acceptable for the existence of a primary fibrocongestive splenomegaly is well established.

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1 Ravenna, P. Banti Syndrome (Fibrocongestive Splenomegaly). Definition, Classification and Pathogenesis, *Arch Int Med* **66** 879 (Oct) 1940.

2 (a) Deve, F. Splénomégalie chronique avec anémie d'origine pyléthrombotique. *Normandie med* **23** 109 (March) 1908. (b) Cauchois, A. Splénomégaties chroniques d'origine pyléthrombotique. Thesis, Paris, no 422, Paris, G. Steinheil, 1908. (c) Warthin, A. S. The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anemia and Banti's Disease, *Internat Clin* **4** 189, 1910.

3 (a) Simmonds, M. Ueber Pfortadersklerose, *Virchows Arch f path Anat* **207** 360 1912. (b) Winkler, H. Ueber primäre Pfortaderthrombose bei Pfortadersklerose und bei chronischen Milz-tumoren, *Frankfurt Ztschr f Path* **17** 377, 1914. (c) Wohlwill, F. Ueber Pfortadersklerose und Bantiahnliche Erkrankungen, *Virchows Arch f path Anat* **254** 243 1925. (d) Freund, M., and Schick, B. A Typical Form of Splenomegaly in Children. Phlebosclerosis of the Portal Circulation, *J Mt Sinai Hosp* **4** 221 (Nov-Dec) 1937.

4 Klemperer, P. Cavernomatous Transformation of the Portal Vein. Its Relation to Banti's Disease, *Arch Path* **6** 353 (Sept) 1928.

5 (a) Davies, J. C. Splenic Anaemia and Portal Thrombosis, *Lancet* **2** 498 (Sept 8) 1928. (b) Villa, L. Zur Diagnose der Milzvenenthrombose, *Med Klin* **25** 909 (June 7) 1929. (c) Moretti, E. Sindromu splenoepatice e splenomegalia tromboflebitica (Contributo anatomo-clinico), *Arch di pat e clin med* **7** 511 (Nov) 1928. (d) Frugoni, C. La splenomegalia tromboflebitica primitiva, *ibid* **3** 574 (Dec) 1924. (e) Brandberg, R. Untersuchungen über splenomegale Leberzirrhosen, sog thrombophlebitische Milztumoren und chronischinfektiöse Milzvergrößerungen unter besonderer Berücksichtigung der Pathogenese und der Behandlungsergebnisse bei Splenektomie, *Acta chir Scandinav (supp 40)* **77** 1 1935. (f) Dameshek, W. Medical Progress. Hematology. *New England J Med* **224** 729 (April 24) 1941.

Rather it seems that the evidence in favor of the occurrence of a splenomegaly caused entirely by passive hyperemia should be critically reexamined

In an earlier study<sup>6</sup> an attempt was made to show that, while the majority of cases reported in the literature as instances of thrombophlebitic splenomegaly should be considered cases of primary splenomegaly complicated by thrombophlebitis, definite evidence for ruling out the possibility that isolated splenic enlargements depended on a primary venous occlusion was still missing. It seems that the solution of this problem lies in the demonstration of splenomegaly entirely due to passive hyperemia. In search of such evidence, the autopsy protocols of Michael Reese Hospital, in Chicago, covering autopsies performed between 1909 and December 1942 were investigated. Cases were chosen in which there was absolute certainty that the venous occlusion was not the result of splenic enlargement and that if splenic enlargement was present it could not be explained as due to some other cause. Thus instances of portal thrombosis occurring in syphilitic or leukemic patients were not considered, for the splenic enlargement could be explained independently of any passive hyperemia.

#### CLASSIFICATION OF CASES

The most common conditions causing chronic passive hyperemia of the spleen are (1) occlusion of the splenic or portal vein (2) chronic heart failure and (3) cirrhosis of the liver.

*Cases with Occlusion of the Splenic or Portal Vein*—In this series there were 12 cases in which occlusion of the splenic or portal vein or both was surely not dependent on a disease of the spleen. The essential data are collected in the accompanying table. In 11 cases the obstruction was due to a tumor, either directly invading the splenic or portal vein or compressing it from the outside. In 1 case a fibrous band produced a stricture of the portal vein. The weight of the spleen was normal in 7 instances, smaller than normal in 3 (respectively 60, 90 and 100 Gm.) and slightly larger than normal in 2 (respectively, 200 and 210 Gm.). In 1 of these 2 cases there was an early hepatic cirrhosis and the enlargement of the spleen, moderate indeed, might have been due to the cirrhosis of the liver.

It is impossible to know the exact time of onset of the venous obstruction in the cases reported here. It can safely be admitted, however, that the occlusion had lasted not less than several days (since at least several days are necessary for a tumor mass to grow so as to obstruct a large vein) and that it was probably several weeks in cases in which both the portal and the splenic vein were occluded by tumor tissue or in which the thrombus showed advanced organization and possibly several months in the instance of portal constriction from an old scar. Since extremely recent occlusions were not included in this series, none of the patients presented the moderate splenic enlargement which occurs immediately after occlusion of the splenic vein but subsides in a few days.<sup>7</sup> Except possibly in 1 case (no. 2), the occlusions were not of very long standing. This fact does not preclude the conclusion to be drawn here, because if no enlargement is manifest within the first few weeks after the establishment of a venous occlusion it is extremely unlikely that it will develop subsequently, at a time when the formation

6 Ravenna, P. La splenomegalia fibroso-congestizia primitiva con cirrosi epatica e la sua sistemazione fra le sindromi bantiene, *Minerva med.* **1** 225 (March 10), 255 (March 17), 276 (March 24), 306 (March 31) 1936.

7 Fieschi, A. Splenotromboflebite acuta e cronica. Studio clinico e istopatologico di un caso operato precocemente e di un caso decorrente da oltre venti anni, *Clin. med. ital.* **70** 133 (Jan-April) 1939.

of collateral pathways and the canalization of the occluded vessel have relieved the circulatory disturbance

In the present material the older age group predominates, and it may be observed that in old age the spleen is less likely to expand. However, 4 patients were less than 34 years old and 1 was 45 years old, and their spleens were not larger than the others'

The average weight of the spleen in the Banti syndrome is more than 1,000 Gm.<sup>8</sup> The average weight of the spleen in these cases of portal obstruction was 140 Gm. The discrepancy is so great that it is difficult to imagine that it can be explained without invoking some factor other than passive hyperemia.

*Cases with Chronic Cardiac Failure*—It is common knowledge that chronic cardiac failure does not produce great and permanent enlargement of the spleen.<sup>9</sup>

*Data on Twelve Cases of Portal Obstruction Independent of Splenic Disease*

Case No.	Sex	Age	Pathologic Diagnosis	Nature of Obstruction	Weight of Spleen, Gm.	Comments
1	M	71	Carcinoma of stomach	Extension of carcinoma into portal vein, organizing thrombosis	90	Ascites, 1,800 cc
2	M	56	Subacute peritonitis	Fibrous band around portal vein	60	Ascites, 2,000 cc
3	F	71	Carcinoma of pancreas	Extension of carcinoma into splenic vein	100	Ascites, 600 cc (recent paracentesis, 3,000 cc)
4	M	64	Carcinoma of pancreas	Partial occlusion from organized thrombosis splenic vein	135	
5	F	33	Retroperitoneal chromaffin tumor	Compression of portal vein by tumor	Normal	
6	F	24	Carcinoma of rectum	Complete occlusion of splenic and portal veins by tumor, splenic vein filled up to hilus of spleen	115	
7	M	32	Carcinoma of pancreas	Obiteration of portal vein by tumor	210	Ascites, 1,500 cc (recent paracentesis, 3,200 cc)
8	F	60	Carcinoma of pancreas	Extension of carcinoma in portal and splenic veins	175	Ascites, 100 cc (recent laparotomy)
9	M	28	Carcinoma of colon	Infiltration of the wall of portal vein	Normal	
10	F	61	Carcinoma of stomach	Metastasis in portal vein	Normal	
11	F	45	Primary carcinoma of liver	Carcinoma metastasis occluding portal vein	200	Early portal cirrhosis, ascites, 1,000 cc, esophageal varices
12	M	57	Carcinoma of stomach	Occlusion of right and left branches of portal vein by tumor	175	Ascites, 2,000 cc

On the contrary, the spleen may be reduced in size (cyanotic atrophy). These facts confirm the statement made many years ago by Oestreich<sup>10</sup> that the size of

8 (a) McMichael, J. The Pathology of Hepatolienal Fibrosis, *J. Path. & Bact.* **39** 481 (Sept.) 1934. (b) Hu, C. H., and Chu, I. K. C. Banti's Disease and Laennec's Cirrhosis. A Clinical and Anatomical Study with Observations on Their Possible Etiological Relationship, *Chinese M. J.*, March 1938, supp., p. 1. (c) Lubarsch, C. Pathologische Anatomie der Milzvergrößerungen, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **40** 527, 1928.

9 (a) Rolleston, H. D., in Discussion on Splenic Enlargements Other Than Leukaemic, *Brit. M. J.* **2** 1157 (Oct. 17) 1908. (b) McNee, J. W. Croonian Lectures on Liver and Spleen. Their Clinical and Pathological Associations, *ibid.* **1** 1017 (June 4), 1068 (June 11), 1111 (June 18) 1932. (c) D'Arrigo, S. Milza da stasi cronica centrale, *Pathologica* **30** 430 (Oct. 15) 1938. (d) Klemperer, P. The Spleen, in Downey, H. *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 3, pp. 1587-1754.

10 Oestreich, R. Die Milzschwellung bei Lebercirrhose, *Virchows Arch. f. path. Anat.* **142** 285, 1895.

the spleen does not give information as to the degree of distention and stasis in the portal venous system

*Cases with Hepatic Cirrhosis*—This condition is mentioned here because it has been affirmed that the splenic enlargement of hepatic cirrhosis offers an example of chronic passive hyperemia of the spleen producing splenic enlargement. There are many arguments, however, against the assumption that this enlargement is due to passive hyperemia alone. The following are the most important: (1) splenic enlargement is frequent, but not constant even in the most advanced stages of the cirrhotic process<sup>11</sup>, (2) enlargement is sometimes present when the cirrhotic changes are, from a mechanical viewpoint, still insignificant<sup>12</sup>, (3) the microscopic appearance of passive hyperemia of the spleen is different from the histologic changes in the same organ in cases of hepatic cirrhosis<sup>13</sup>, (4) in experimental cirrhosis splenic enlargement preceded portal stasis<sup>14</sup>, and (5) enlargement occurred when the spleen was dissociated from the portal circulation and implanted in the subcutaneous tissue of the abdomen (marsupialized spleen)<sup>15</sup>, (6) in cases of portal cirrhosis complicated by portal thrombosis, as in the instances collected by Reich,<sup>16</sup> the splenic enlargement could easily be explained on the basis of the cirrhotic process alone, since it was not constant, was of moderate size and seemed to occur with the same frequency as in cases of uncomplicated hepatic cirrhosis.

Thus the results of study of the size of the spleen in hepatic cirrhosis are not contributory to the question of splenomegaly exclusively due to passive hyperemia.

#### COMMENT

The 12 instances of portal obstruction reported on here speak against the possibility that passive hyperemia alone may produce a splenic enlargement of long duration and of some importance. As long ago as 1908, Osler<sup>17</sup> remarked that neither splenomegaly nor anemia is a special feature in cases of long-standing obliteration of the portal vein. Other authors<sup>18</sup> reported instances of portal thrombosis not accompanied by splenic enlargement. Lack of correlation between stenosis of the portal vein and splenomegaly was noticed also by Simmonds<sup>3a</sup> in 7 cases.

11 Klempere<sup>9d</sup> Lubarsch<sup>8c</sup>

12 (a) Banti, G. Ueber Morbus Banti, *Folia haemat* **10** 33, 1910. (b) Cushing, H., and MacCallum, W. G. Two Cases of Splenectomy for Splenic Anemia. Report on Pathologic Changes in Splenic Anemia, *Arch Surg* **1** 1 (July) 1920. (c) Oestreich<sup>10</sup>. (d) McNee<sup>9b</sup>. (e) Brandberg<sup>5c</sup>.

13 Jager, E. Milzbau und Kreislaufstörung. I. Ein Beitrag zur Entstehung von Milzveränderungen bei Stauungszuständen im Pfortadersystem, *Virchows Arch f path Anat* **299** 531, 1937. Oestreich<sup>10</sup>. Klempere<sup>9d</sup>.

14 Menon, T. B. The Splenic Reaction in Experimental Cirrhosis and in Precirrhotic Intoxication, *J Path & Bact* **46** 521 (May) 1938.

15 Cameron, G. R., and De Saram, G. S. W. A Method for Permanently Dissociating the Spleen from the Portal Circulation (the "Marsupialized" Spleen) and Its Use in the Study of Experimental Liver Cirrhosis, *J Path & Bact* **48** 41 (Jan) 1939.

16 Reich, N. E. Portal System Thrombosis Occurring in Portal Hypertension, *Ann Int Med* **17** 270 (Aug) 1942.

17 Osler, W., in Discussion on Splenic Enlargements Other Than Leukaemic, *Brit M J* **2** 1151 (Oct 17) 1908.

18 (a) Christeller, E., and Puskeppelles, M. Die peri-arteriellen Eisen- und Kalkinkrustationen in der Milz, *Virchows Arch f path Anat* **250** 107, 1924. (b) Franke, H. Zur Diagnose der trunkularen und terminalen Pfortaderthrombose, *Med Klin* **35** 1601 (Dec 15), 1632 (Dec 22) 1939. (c) Borrmann. Beiträge zur Thrombose der Pfortaderstämme, *Deutsches Arch f klin Med* **59** 283, 1897. (d) Weir, J. F., and Beaver, D. C. Diseases of the Portal Vein. A Review of One Hundred and Twenty-Seven Instances, *Am J Digest Dis & Nutrition* **1** 498 (Sept) 1934. (e) Lubarsch<sup>8c</sup>. (f) Wohlwill<sup>3c</sup>.



All these observations, however, were overshadowed by the fact that too often in the literature on portal obstruction the size of the spleen was mentioned only if there was a marked enlargement. Thus, in a study of 68 cases of occlusion of the portal vein Lissauer<sup>19</sup> reported the following splenic changes: leukemia in 1, perisplenitis in 2, splenic abscesses in 2 and total infarction in 1. The spleen was not mentioned in the reports of the remaining 62 cases. More recently 21 instances of portal obstruction from various causes (including 6 of obstruction due to cancer) were collected by Webster.<sup>20</sup> The splenic weight was given in 1 case only, in which it was 2,400 Gm. and the diagnosis of Banti's disease had been made. Incidentally the thrombus was recent and could not have been the cause of the splenic enlargement. The size of the spleen was also not stated in 7 of 8 instances of portal thrombosis confirmed at autopsy reported by Pallette.<sup>21</sup> In the remaining case in which the condition had been diagnosed as Banti's disease, the thrombus was recent and was believed to be a sequel of splenectomy. This tendency to call attention to the spleen if it is enlarged and not to mention it otherwise may be partly responsible for the general impression that portal thrombosis is a cause of splenomegaly.

A splenic enlargement of long duration could not be obtained in experimental animals by producing passive hyperemia of the spleen. Warthin's<sup>22</sup> experiments were among the first. By ligation of the splenic vein in dogs and rabbits he obtained an early enlargement, followed by permanent atrophy of the spleen. Consistently similar results were observed more recently,<sup>22</sup> even when the obstruction was applied progressively or intermittently. Passive hyperemia of the liver and of the portal venous system may also be obtained by ligation of the hepatic artery, even here, after an early enlargement of a few days' duration, atrophy of the spleen ensued.<sup>23</sup> One should therefore conclude with Menon<sup>22a</sup> that these experiments do not support, but seem to negate, the view that the Banti syndrome is due to blockage of the portal vein. The only discordant opinion was formulated by Rousselot and Thompson.<sup>22b</sup> These authors obtained a cirrhosis of the liver and a lasting splenic enlargement in dogs after repeated injections of small particles of silicon dioxide (silica) into the portal vein. However, some of the particles were eventually found in the spleen itself. Thus some direct damage to the spleen could not be ruled out, and the authors' contention that passive hyperemia alone was responsible for the splenic enlargement was not proved.

The idea that passive hyperemia alone is sufficient to produce a chronic splenomegaly was based on a mere coincidence. In most instances fibrocongestive splenomegaly was accompanied by portal venous sclerosis (Banti<sup>24</sup> called it endophlebitis), and this could give origin to a venous thrombosis.<sup>25</sup> When autopsy

19 Lissauer, L. Beitrag zur Frage der Entstehung der Pfortaderthrombose, *Virchows Arch f path Anat* **192** 279, 1908.

20 Webster, L. T. Portal Thrombosis, *Bull Johns Hopkins Hosp* **32** 16 (Jan) 1921.

21 Pallette, E. C. Portal Thrombosis, *California & West Med* **45** 324 (Oct) 1936.

22 (a) Menon, T. B. Venous Splenomegaly. A Study in Experimental Portal Congestion, *J Path & Bact* **46** 357 (March) 1938. (b) Rousselot, L. M., and Thompson, W. P. Experimental Production of Congestive Splenomegaly, *Proc Soc Exper Biol & Med* **40** 705 (April) 1939. (c) Castiglioni, G., and Pepere, M. Ricerche sperimentali intese a modificare il circolo splenico, *Arch ital di anat e istol pat* **11** 14 (Dec) 1939.

23 Patrassi, G., and Baggio, G. L'arteria epatica come fattore propulsivo del circolo portale. Su alcuni effetti della legatura dell'arteria epatica sugli organi splancnici, *Sperimentale, Arch di biol* **99** 361, 1939.

24 Banti, G. La splenomegalia con cirrosi epatica, *Sperimentale (sez biol)* **48** 407, 1894.

25 Rosenthal, N. Clinical and Hematologic Studies on Banti's Disease. I. The Blood Platelet Factor with Reference to Splenectomy, *J A M A* **84** 1867 (June 20) 1925. Nägeli,

was performed after the splenomegaly had lasted a number of years, the venous changes often were so pronounced that it could be easily assumed that they were the oldest and the primary lesions. It may be of interest in this respect to mention the report of Wallgren<sup>26</sup>. He described 4 patients with fibrocongestive splenomegaly in all of whom the portal vessels were normal. Nevertheless, being unable to explain the splenic enlargement otherwise, he postulated that a portal stenosis must have been present and described his cases as instances of "chronic splenic pylephlebotenosis."

Even when both the cause of the splenic enlargement and that of the portal obstruction are unknown, a complete pathologic examination and a consideration of the pathologic and clinical data will frequently show that the portal obstruction is not the cause of the splenomegaly. In each individual case different elements should be considered, but the venous occlusion should not be assumed to be the primary cause of the circulatory disturbance in the portal bed if (1) the occlusion is located outside the portal or splenic vein (e. g. in the gastric or mesenteric veins) and therefore does not hinder the venous return from the spleen, (2) the occlusion is located in the splenic or portal vein but (a) there are large anomalous anastomoses between the splenic and the left renal vein (providing adequate collateral circulation from the spleen into the renal vein), (b) the occlusion is due to a thrombus situated in a dilated or clearly aneurysmal segment of the vein (which makes it likely that the vein was damaged previously and that the thrombosis is a secondary phenomenon), (c) the occlusion is due to a recent thrombus, while the splenomegaly is known to have lasted a long time, (d) the vein involved is tortuous and dilated not only distally but beyond the obstructed segment (which indicates that the portal hypertension occurred independently and probably before the venous obstruction) or (e) the splenic artery is dilated (this is important, since venous obstruction of any degree cannot cause dilatation of a large artery and this possibility is even more remote in the case of the spleen, for backward perfusion of this organ is impossible<sup>27</sup>), (3) the occlusion is due to a trauma and it is not excluded that this produced some lesions of the vasomotor nerves of the spleen, thereby causing active splenic hyperemia (this point will be discussed further in this study) or (4) there are signs of exaggerated splenic activity, such as (a) delayed physical development (so-called splenic infantilism), (b) leukopenia with relative monocytosis and lymphocytosis or/and (c) anemia due to depressed activity of the bone marrow or to excessive hemolysis. Increased activity of the spleen may indeed be a consequence of active hyperemia of this organ, but not of passive hyperemia.

Reviewing the literature on splenomegalies, I did not find a single instance in which the diagnosis of splenomegaly of passive hyperemia may be sustained if the aforementioned diagnostic criteria are used. In the great majority of cases the anatomic description of the vessels and organs involved is so incomplete that a critical evaluation is impossible. In a few others it can be definitely stated that

P Die Klinik der chronischen Megalosplenien, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40** 511, 1828. Gregoire, R. Pyléthrombose et splenectomie, Sang **9** 761, 1935. Mouroud Olmer, J., and Jouve, A. X. Splénomégalie scléreuse avec gastrorragies. Splenectomie suivie de thrombose porto-mésentérique tardive, Mem. Acad. de chir. **63** 543 (April 21) 1937. Davies<sup>51</sup>. Ravenna<sup>6</sup>. Brandberg<sup>50</sup>.

<sup>26</sup> Wallgren, A. Contribution à l'étude des splénomégaties de l'enfance (Pyléphléboténose splénique), Acta pædiat. (suppl.) **7**:1, 1927.

<sup>27</sup> Guillery, H. and Petersen, H. Untersuchungen über die Funktionen der Milz. IV. Die Blutaufnahme und -abgabe und die Blutsperrern der Milz, Ztschr. f. d. ges. exper. Med. **101** 683, 1937.

the diagnosis was erroneous, as for instance when the diagnosis of thrombophlebitic splenomegaly was made and the thrombus was located in the superior mesenteric vein,<sup>28</sup> the occluded vein was dilated beyond the obstructed segment,<sup>29</sup> a large anomalous anastomotic vein connected the splenic and left renal veins,<sup>30</sup> apparently providing adequate collateral circulation, or, finally the splenic artery was described as greatly dilated.<sup>31</sup>

If all possible diagnostic criteria are used to differentiate between splenomegaly due to passive hyperemia and splenomegaly complicated by portal obstruction, I believe that in most cases the enlargement will be classified as belonging to the latter type. In a few instances it may not be possible to decide anatomically whether the portal obstruction preceded or followed the splenomegaly, and in some exceptional case it may even be clear that the portal obstruction preceded. To classify these instances properly it is well to remember that neither pathologic nor experimental evidence supports the possibility of a chronic splenomegaly exclusively due to passive hyperemia.

For instance, a case is on record<sup>32</sup> in which the splenic enlargement developed after a trauma which also caused constriction of the splenic vein. During splenectomy the "portal vessels" were seen to be tortuous and dilated. Since the obstruction of the splenic vein did not prevent a dilatation of the veins distal to the obstacle, it could not have had a determining effect in the production of the splenic hyperemia. Rather, it seems likely that the mechanism was a lesion (compression, severance) of the splenic nerves running alongside the splenic artery and that the consequent vasomotor paralysis produced active hyperemia of the spleen.

The assumption that the splenomegaly in Banti's syndrome may be due to a lesion of the nerves of the spleen was proposed by Bari.<sup>33</sup> In the autopsy protocols of Michael Reese Hospital I found the description of a case which seems to substantiate this hypothesis.

The patient was a girl who at the age of 3½ years fell out of bed and immediately afterward complained of violent abdominal pain. Two weeks later she had a sudden hematemesis, which recurred several times during the following years. When she was 11 years old an enlarged fibrocongestive spleen was removed but the gastric hemorrhages recurred after the operation, causing death one year later. At the autopsy an eroded varicose vein near the cardiac end of the stomach was interpreted as the cause of the final hemorrhage. The mechanism of the portal

28 Lucchi, G. Morbo di Banti a lentissimo decorso e splenomegalia tromboflebitica con trombosi della vena mesenterica superiore, *Riv di clin med* **35** 421 (July 15) 1934.

29 Dubois-Roquebert and Sigault. Splenomegalie thrombophlebitique, *Mem Acad de chir* **66** 295 (Feb 28-March 6) 1940.

30 Arrigoni, A. Anemia emolitica, secondaria a reticolo-endoteliosi sistemica, subentrante a sindrome tromboflebitica della splenica, *Med ital* **16** 531 (Aug) 1935. Simonds, J. P. Chronic Occlusion of the Portal Vein, *Arch Surg* **33** 397 (Sept) 1936. Hantz, E., and Romhányi, G. Stenose der Vena portae mit Symptomen der Thrombose der Vena lienalis, *Ztschr f klin Med* **135** 66, 1938.

31 (a) Onsy, A. B. The Pathogenesis of Endemic (Egyptian) Splenomegaly, *Tr Roy Soc Trop Med & Hyg* **30** 583 (April) 1937. (b) Olmer, J., Vague, J., and Dumou-Legré, M. Splenopathie cirrhotique avec calcification de la veine splénique, *Ann d'anat path* **16** 905 (July) 1939. (c) Christeller and Puskepples.<sup>18a</sup> (d) Edens. Ueber Milzvenenthrombose, Pfortaderthrombose und bantische Krankheit, *Mitt a d Grenzgeb d Med u Chir* **18** 59, 1908. (e) Brahme, L. Ein Fall von chronischen Pfortaderthrombose, *Acta med Scandinav* **61** 175, 1924.

32 Thompson, W. P. The Pathogenesis of Banti's Disease, *Ann Int Med* **14** 255 (Aug) 1940.

33 Barr, J. Three Cases of Banti's Disease, *Lancet* **2** 493 (Aug 23) 1902.

hypertension causing the gastric varices was not explained at autopsy, for no obstacle whatsoever was seen in the portal venous system or in the liver

The case presents a striking similarity to an instance reported by Cesa-Bianchi and Cellina<sup>34</sup> Their patient was a healthy boy who at the age of 9 years fell and received a violent contusion in the abdomen Twelve hours later he had a severe hematemesis At that time splenomegaly and anemia with leukopenia were found After two years of relative well-being he had a sudden hematemesis, which was followed by death At autopsy, a fibrocongestive splenomegaly with many sclerosidrotic nodules was noted, but no obstacle to the portal flow A few small patches of intimal thickening represented the only lesion of the portal venous system The possibility that the trauma was responsible for a lesion of the nervous system producing splenic congestion must be seriously considered in these instances This splenomegaly would have the same origin as the splenic enlargement obtained experimentally by denervation of the spleen<sup>35</sup> A nervous mechanism might also be responsible for the splenomegaly in cases in which the disease developed in patients with adrenal deficiency<sup>36</sup> This would explain the rapid and marked reduction of splenic size obtained in some instances by repeatedly injecting epinephrine hydrochloride intravenously

In the pathogenesis of fibrocongestive splenomegaly, however, a purely nervous mechanism is probably rather infrequent In most instances the splenic enlargement is due to toxic, infectious or parasitic damage to the splenic parenchyma itself<sup>1</sup>

It is impossible to say at present how many examples of the Banti syndrome previously classified as splenomegaly caused by passive hyperemia were due to an infection of the spleen The difficulty lies in the fact that, even in known specific infections and infestations, the finding of the etiologic agent and of inflammatory lesions in the spleen is extremely rare The development of the knowledge of the pathogenesis of schistosomal splenomegaly offers an interesting example of the difficulties involved This disease was called "endemic Egyptian splenomegaly," and as long as its cause was unknown it was considered identical with Banti's disease When ova of *Schistosoma* were found in the livers of many patients, it was thought that the splenomegaly was the consequence of passive hyperemia due to parasitic obstruction of the portal vein Finally, by means of more accurate and extensive research,<sup>31a</sup> ova were found inside the spleen itself, but in small number and showing advanced regressive changes It was also noticed that the splenic artery was greatly dilated Therefore it seems that, though the spleen rapidly destroys the parasite, parenchymal changes ensue, which are responsible for the splenic enlargement Portal obstruction, which occurs rarely and late in this condition, should be a factor of little, if any, importance

34 Cesa Bianchi, D, and Cellina, M Morbo di Banti e sindromi affini, Rome, Luigi Pozzi, 1939

35 von Tarchanoff, F Ueber die Innervation der Milz und deren Beziehung zur Leucocythämie, Arch f d ges Physiol 8 97, 1874 Henschen, C, and Howald, R Die anatomischen und klinisch-physiologischen Folgen der operativen Entnervung der Milz Experimentelle Untersuchungen, Arch f klin Chir 157 667, 1929 Barcroft, J, and Elliott, R H E Some Observation on the Denervated Spleen, J Physiol 87 189 (July) 1936 Pasqualino, G Ricerche preliminari sulla provocazione di una possibile ipersplenemia terapeutica, Biochim e terap sper 25 327 (July 31) 1938 Sugimura, M Ueber Milzentnervung, Arch f klin Chir 197.169, 1939

36 Galluppi, A Malattia di Banti e affezioni sistematizzate del reticolo-endotelio, Clin med ital 60 183 (May-June) 1929 Cesaris Demel, V Considerazioni sull'atonía dell'apparato muscolare contrattile della milza nella patogenesi di alcune splenomegalie, Baglivi 1-200, 1935 Lenzi, F Sindrome bantiana Splenomegalia fibroso-congestizia prevalentemente fibrosa (contributo clinico, ipotesi patogenetiche), Haematologica 22 47, 1940

## SUMMARY AND CONCLUSIONS

The assumption that fibrocongestive splenomegaly may be due to passive hyperemia is not satisfactory, because it fails to explain several facts observed in this condition. Only the finding of some type of venous obstruction in a large number of cases of fibrocongestive splenomegaly seems to speak in favor of passive hyperemia as cause of splenomegaly. However, such obstruction was missing in several cases, and if present it was found in late stages of the disease. There are several often overlooked signs which may be of assistance in deciding whether the obstruction preceded or followed the onset of the splenic enlargement.

In 12 consecutive instances in which portal obstruction was surely independent of a splenic disease the spleen was not appreciably larger than normal. In 3 of them it was smaller than normal. This agrees with the observations that the experimental ligation of the splenic vein produces not enlargement but atrophy of the spleen and that chronic passive hyperemia due to cardiac failure does not cause marked enlargement of the spleen and often induces its atrophy.

It is therefore concluded that (1) passive hyperemia alone is not sufficient for the production of chronic splenic enlargement, (2) obstruction of the portal venous circulation in cases of fibrocongestive splenomegaly represents not the cause but a complication of the splenic disease, and (3) terms such as primary splenic thrombophlebitis, phleboscrosis, phlebotenosis, carcinomatous transformation of the portal vein with secondary splenomegaly and splenomegaly of passive hyperemia are misnomers, because they represent an erroneous conception as to pathogenesis, and should not be used. In most of the cases collected under such headings the splenomegaly constitutes the primary change.

# REVIEW OF NEUROPSYCHIATRY FOR 1943

STANLEY COBB, M D

BOSTON

## MOTONEURON

At the termination of every reflex arc we find a final neurone, the ultimate conductive link to an effector organ, gland, or muscle. This last link in the chain—e g, the motoneurone—differs obviously in one important respect from the first link in the chain. It does not subserve exclusively impulses generated at one single receptive source alone, but receives impulses from many receptive sources situate in many and various regions of the body.

Thus in 1904 Sherrington<sup>1</sup> described the “final common path” of nervous impulses from anterior horn cell in the spinal cord to motor end plate in the striated muscle. On his work depends most of the knowledge of the reflex function of cord and muscle, and recent work is largely elaboration of what he began. During the last two years several important discoveries have been made in this field.

In the first place, Elliott<sup>2</sup> has shown that the distribution of the somatic motor cells of the ventral gray columns of the spinal cord is not as usually described by anatomists. These cells, which, with their axons, constitute the final common pathway to the voluntary muscles, were usually considered to have a segmental distribution even in the lumbosacral and cervical enlargements. At the center of a spinal segment there was supposed to be a mass of cells that spindled off at the limits of the segment, so that a picture of one of the cell columns would look like a string of spindle-shaped beads. Elliott found that this is not the case, the motor cells in the adult human cord are arranged in long nuclear masses which are not segmentally determined but have conspicuous functional relationships. For example, the long medial mass in the cervical and lumbar regions serves the sacrospinalis and other trunk muscles, while the lateral masses serve the arms and legs.

The motoneuron does not have the simple reflex connections that neurologists show in diagrams of spinal reflex arcs. Sherrington conceived of a “motoneurone pool” in the spinal gray matter into which motor tracts and reflex arcs discharged. From the histologic standpoint this takes in a group of ventral horn cells and the many small internuncial neurons clustered about them. Most motor tracts from above, discharging on the internuncial cells, make a reflex arc of more than three neurons. Lloyd,<sup>3</sup> at the Rockefeller Institute, has applied micro-oscillographic leads to various areas of the spinal gray matter, and by physiologic analysis of the electro-neurograms has been able to show that the pyramidal tract plays on these internuncial neurons in at least three regions of the gray matter. He has also been able to distinguish<sup>4</sup> between the discharges of large and of small myelinated fibers and between the discharges of reflex arcs made up of only two neurons and those made up of several neurons. The simple two neuron arc consists of a large fiber from a muscle which connects directly with a ventral horn cell. These arcs mediate

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1 Denny-Brown, D. Selected Writings of Sir Charles Sherrington, New York: Paul B. Hoeber, Inc., 1940.

2 Elliott, H. C. 'Am. J. Anat.' **70** 95, 1942.

3 Lloyd, D. P. C. J. Neurophysiol. **4** 525, 1941.

4 Lloyd, D. P. C. J. Neurophysiol. (a) **6** 111 and 143, 1943, (b) **6** 293 and 317, 1943.

myotatic reflexes. Moreover, reflex activity over extensor two neuron arcs is inhibited by the action of the multineuron arcs. In some experiments the activity of the internuncial neurons was suspended by pyramidal tract discharges. This suggests that the mechanism for reciprocal innervation may lie in the premotoneuron internuncial system. McCouch<sup>5</sup> supports such a hypothesis by finding that in spinal reflexes the locus of inhibition seems to be in the internuncial neurons. Thus the experimenters with this intricate electrophysiologic technic are slowly piecing together the puzzle, when the picture is complete the physiologist will be able to understand motor facilitation, inhibition and reciprocal movement. The clinician may have a better understanding of flaccid paralysis, spasm, incoordination, clonus and tremor.

Paul Weiss<sup>6</sup> has for several years been working on the mechanics of nerve growth in the zoologic laboratories of the University of Chicago. This subject is well summarized in the third growth symposium,<sup>6</sup> and references are there given to his detailed work in various biologic journals. The important point is that recent experiments on living nerve tissue, beginning with those of Harrison<sup>7</sup> and ending with those of Weiss, have shown that the former theories of neurobiotaxis and chemotaxis do not hold, axons do not grow out to reach their appropriate end organ because of some mysterious humor that attracts them thereto. The peripheral end of the growing or regenerating axon sends off large numbers of fine protoplasmic filaments. A few of these find their way to the muscle (if it is a motor nerve), and after functional connection is established the other, unsuccessful filaments degenerate. Just what chemical reaction causes this phenomenon is not known, but similar reactions are known in other biologic processes. In the case of the axon that is regenerating after injury, the task of the many wandering filaments is to find the old pathway to the distant muscle. This path lies in the nerve sheaths left empty when the axons degenerated. Some of the axons find these old tubes and grow down into them simply because it is the path of least resistance. The process is determined by numerical chance and mechanical advantage. In his most recent work, stimulated by the war, Weiss<sup>8</sup> has developed new methods of nerve splicing and nerve grafting. Sutureless splicing can be accomplished by joining the ends of the severed nerve in a sleeve of fresh or frozen and dried artery,<sup>9</sup> thus guiding the axons to the proper channel. Also pieces of nerve can be frozen and dried and stored for later use as nerve grafts.

Young,<sup>10</sup> in the department of zoology at Oxford, has also been working on the process of regeneration in nerve and muscle. He summarized his work in a paper at the last meeting of the American Neurological Association. His experiments complement those of Weiss. He has shown that in surgical union of nerves containing large and small fibers the diameter of the regenerating fibers depends on the volume of the protoplasmic nerve outgrowths ("axoplasm") and on the size of the tubes in the peripheral stump into which they flow. Motor branches of a mixed nerve regenerate larger fibers than the sensory branches. It is important to have the receiving tubes of the stump large enough to receive the motor filaments, so the suture must not be delayed too long lest the peripheral stump atrophy and shrink, and if a graft is used a nerve must be chosen with large enough tubes

5 McCouch, G. P., Hughes, J., and Stewart, W. B. *J. Neurophysiol.* **4**: 547, 1941.

6 Weiss, P. *Growth (supp.)* **5**: 163, 1941.

7 Harrison, R. G. *Proc. Roy. Soc., London s. B.* **118**: 155, 1935.

8 Weiss, P. *Tr. Am. Neurol. A.*, 1943, to be published.

9 Weiss, P., and Davis, H. *J. Neurophysiol.* **6**: 269, 1943.

10 Young, J. Z. *Tr. Am. Neurol. A.*, 1943, to be published.



Size is important also, because no function returns until the fibers gain an adequate diameter. This takes thirty-seven days in the nearest part of the peripheral stump in a rabbit. In man the process is probably slower, so there is considerable delay in the start of regeneration, even under the best conditions. Once started, the functionally complete regeneration advances at the rate of 2.6 mm per day. In man the rate is variable, the old estimate of 1 mm per day is probably too slow. Fibers arriving at unatrophied muscle innervate the old end plates immediately, if regeneration is delayed the old end plates atrophy and new ones must be made. This is a slow process, and if regeneration of the nerve is too long delayed the atrophied muscle may never completely recover.

#### MUSCLE AND MYONEURAL JUNCTION

Carey<sup>11</sup> has been studying muscle and motor end plates. His investigations into the morphology and mechanics of the cross striations of skeletal muscle seem to finally get rid of the "sarcomere," which he considers "a morphological myth which has existed in the literature for over 100 years." Molecular pressure waves in the minute tubular structure of the muscle seem to be responsible for the different appearances seen, physical and chemical conditions varying with function, therefore determine the appearance of the "striations." The variations in structure seen in degenerating muscles are structural not in the histologic but in the biochemical sense. Carey's work on the end plates<sup>12</sup> is of even more importance for understanding the physiology and pathology of the motoneuron. He has observed that the motor nerve plates in skeletal muscle enlarge when the muscle is stimulated to great activity, often they spread out to twice their normal size. Moreover, they change rapidly as the muscle works, expanding as the muscle contracts and retracting as it relaxes. The increase in surface area of the plate may favor the transmission of the nerve impulse to the muscle substance by increase of the surface area of the plate. The retracted motor nerve plates are related to muscle fibers with coarse, widely spaced striations, the expanded plates are related to fine, closely spaced cross striations. These structural changes suggest the correctness of the chemical theory of the transmission of the nerve impulse.

Fulton and Nachmansohn<sup>13</sup> have developed a new concept of the transmission of the nerve impulse, in axons as well as across synapses and across the myoneural junction (end plate to sarcoplasm). The "electrical" and "chemical" theories of transmission are conciliated by showing that acetylcholine can be metabolized at as high a rate as is required by the assumption that it is a transmitter of nerve impulses known to pass the myoneural junction in a few milliseconds. Actually it was the enzyme choline esterase with which Nachmansohn worked, and he showed in some remarkable experiments on the electric organs of fishes and the giant axons of squids that the concentration of choline esterase is sufficiently high to indicate that acetylcholine is formed and metabolizes at a rate sufficiently rapid to propagate an impulse along axons at a rate compatible with observed nerve transmission. Moreover, the acetylcholine metabolism is intrinsically connected with the electrical discharge, there being found a close parallelism between the voltage of the action potentials and the concentration of choline esterase.

11 Carey, E. J., Zeit, W., and Massopust, L. *Am J Anat* **70** 119, 1942, Wave Mechanics in Striated Muscle. Effects of Experimental Variations in Temperature and of Microcapillarity on Cross Striations in Muscle, *Arch Path* **30**:1041 (Nov.) 1940.

12 Carey, E. J. *Am J Path* **18** 237, 1942.

13 Fulton, J. F., and Nachmansohn, D. *Science* **97** 569, 1943.



All these new observations bring the physiologist nearer to an understanding of the contraction of muscle, which Fenn<sup>11</sup> has vigorously described in his monograph

Unlike other cells, however, the muscle cell can be conveniently stimulated to contraction, thereby bringing about an almost instantaneous transformation of its shape and its cytology, its mechanical and electrical state, its temperature, chemical composition and rate of respiration. Thus at the desire of the experimenter a whole series of new chemical reactions can be thrown into activity in an orderly and reproducible manner. This sudden transformation so produced may be properly described as an explosion. The muscle is a self-cocking explosive machine with a convenient trigger. The explosion turns chemical potential energy into mechanical energy. Thus the machine is useful. We can use it to heave rocks, sew on buttons, or for the still more delicate task of dissecting another muscle from the leg of a fly. It has a highly orderly structure of both microscopic and sub-microscopic dimensions. Many refined optical methods are available for the examination of this structure and the changes incident to the contraction. The forces developed in a muscle "explosion" are of amazing magnitude. Some of our tendons transmit forces of the order of half a ton. Single fibers of the muscle can also be isolated in Ringer's solution by painstaking dissection, and the resulting threads of muscle contract vigorously for days and exert relatively large forces.

The great enigma, however, remains unsolved. How is the chemical energy transformed into mechanical energy?

#### RELATION TO THE PROBLEMS OF POLIOMYELITIS

It is obvious that all phenomena of the motoneuron, myoneural junction and muscle are important for the understanding of infantile paralysis (poliomyelitis). Within the last two years the "Kenny treatment"<sup>15</sup> for acute and chronic poliomyelitis has become famous. It was at first empiric, but it is now based on a concept of pathology and dysfunction quite at variance with the orthodox understanding of the process. The adherents of the Kenny theory consider that infantile paralysis does harm by "spasm" of the affected muscles, not by flaccid paralysis. The antagonistic muscles are said to show "alienation" and unless retrained may permanently lose function. Other muscles are said to show "incoordination." Treatment is directed especially at the muscles in "spasm," because allowing the spastic state to continue is supposed to cause the paralysis. Some physicians have accepted the "Kenny concept" to a greater or less extent. Kabat and Knapp<sup>16</sup> have studied the "muscle spasm" in acute poliomyelitis and explain it as a release phenomenon, caused by lesions of the internuncial neurons in the spinal gray matter, with sparing of the ventral horn cells. They do not, however, explain what is released to cause the spasm. They seem to imply that the ventral horn cell itself is set free from its connecting neurons and thus goes into excessive activity—an unheard-of sort of neuropsychologic activity, because motor nerve cells need something to set them off, they are units depending on reflex stimulation and if left alone do not go on discharging. They also overlook the possibility that the lesions of the gray matter and meninges may act on the motor nerve cells and their axons as direct irritants, causing acute stimulation for a time. Perhaps the simple two neuron arcs of Lloyd<sup>17</sup> are released when the internuncial neurons are injured, but this mechanism at best would produce a very slight postural contraction of the muscle. The main thesis of Kabat and Knapp's paper is that prostigmine causes relaxation of the muscle spasms of poliomyelitis and makes for more rapid recovery.

14 Fenn, W. O. Muscle, in Cattell, J. Biological Symposia, Lancaster, Pa., Jaques Cattell Press, 1941, vol. 3, p. 2.

15 Pohl, J. F., and Kenny, E. Kenny Concept of Infantile Paralysis and Its Treatment, Minneapolis, Bruce Publishing Co., 1943.

16 Kabat, H., and Knapp, M. E. The Use of Prostigmine in the Treatment of Poliomyelitis, J. A. M. A. 122:989 (Aug. 7) 1943.

Their data on this point are certainly suggestive, but with the many variables in recovery rate and the fact that hot fomentations were also used, they seem hardly justified in stating that "the drug significantly increased the range of passive motion, decreased or eliminated deformities in some instances by relaxation of hypertonus and in some cases improved active motion"<sup>16</sup> Just how the postigmine might act to give these results is not clear In all probability the use of prostigmine can be looked on as a method of setting free more acetylcholine by inhibiting choline esterase One would expect this to increase the function over the remaining reflex arcs, rather than diminish it

At the New York Neurological Institute spasm of muscles and degeneration were studied by Moldaver<sup>17</sup> in 49 cases of poliomyelitis He used the electrical methods of measuring chronaxia and making electromyograms He controverts quite flatly the Kenny findings Using objective methods, he has found that "muscle spasm" does not lead to neuromuscular degeneration and that the antagonists of the involved muscles, the "alienated muscles," have lost power because of damage to the motoneuron in the cord The "incoordination," if found at all, is not what neurologists recognize under that name, but the effect of partial paralysis

Watkins, Brazier and Schwab,<sup>18</sup> working independently and using different but equally sound objective electrophysiologic methods, also disagree with the "Kenny concept" of the pathologic process in poliomyelitis They summarize their findings by saying

1 In poliomyelitis the term "muscle spasm" is inadequate to describe the complexity of dysfunction which is revealed by electromyography

2 In the acute stage, only muscles with some degree of paralysis discharge electrical potentials at rest, these electrical abnormalities are not correlated with the presence of clinical "spasm"

3 Partially paralyzed muscles are hyperirritable to passive stretching as indicated by electrical discharges and pain, the muscle tension thus developed appears to be a reflex protective mechanism

4 The electrical activity in paretic muscles at rest increases during the period of improving motor power, and the pattern of discharges corresponds with that seen in muscles during regeneration of peripheral nerves When improvement in motor power ceases, spontaneous electrical discharges disappear

5 No abnormal electrical activity is associated with the muscle contractures of the late stage of poliomyelitis, nor are any discharges present in completely paralyzed muscles

6 The concept of "mental alienation" does not contribute to the explanation of paresis in our cases, since objective signs of a disease process were always present in the paretic antagonists of muscles in "spasm"

7 Increase of voltage of action potentials during successive ergographic tests is an index of recovery of motor power

8 Of the three concepts of Kenny, the only one upheld by our objective measurements is that of "incoordination," although the term is misleading We demonstrated not only simultaneous activation of protagonists and antagonists, but also intermittent synchrony of individual discharges from opposing muscles, such as is found in peripheral nerve injuries during regeneration of axons Disordered reciprocal innervation seems to be a more descriptive term for this type of dysfunction

Thus it is being demonstrated once more in the history of medicine that new and empiric methods of treatment, backed by uncritical enthusiasm, may produce many cures but much physiologic nonsense The treatment may be good, but the ex post facto rationalizations of the therapist are usually bad

<sup>17</sup> Moldaver, J Physiopathologic Aspect of the Disorders of Muscles in Infantile Paralysis, J A M A 123 74 (Sept 11) 1943

<sup>18</sup> Watkins, A, Brazier, M A B, and Schwab, R S Concept of Muscle Dysfunction in Poliomyelitis, Based on Electromyographic Studies, J A M A 123 188 (Sept 25) 1943

## MYASTHENIA GRAVIS

It has been known for years that the thymus gland is hyperplastic or neoplastic in about half the cases of myasthenia gravis. Irradiation with roentgen rays was tried some years ago, but the therapeutic effect was found to be variable. In a few cases there was improvement, in the majority there was none. Not until the last eight years had thoracic surgery advanced to a point where operative removal of the thymus might be tried. Blalock and his colleagues<sup>19</sup> at first removed a cystic tumor from the thymus with relief of myasthenia and then turned their attention to operation on thymic glands that showed no disease by clinical or roentgenographic examination. Six patients were treated by removal of all surgically available thymus tissue. In 5 of these the tissue was considered hyperplastic. Three of the patients have shown continued improvement in their myasthenic symptoms.

These results should not be considered discouraging if they are compared with the early work on removal of the thyroid and the parathyroids. Roentgen irradiation was tried in this field and found wanting because of the unpredictability of the results. Surgical removal was at first moderately successful and is now satisfactory. With myasthenia gravis it may well be that the disappointing cases are those in which thymic tissue not only lies in the substernal region but has spread into less surgically accessible areas. Patients whose cases suggested this have been operated on by Cope at the Massachusetts General Hospital.<sup>20</sup>

Viets has been carrying on a systematic study of myasthenia gravis from the medical and neurologic standpoints. By running a special outpatient clinic, he has kept a large group of these relatively rare patients, and has been able to make many observations. With Schwab<sup>21</sup> he has worked out a diagnostic test by the use of prostigmine. A dose of 1.5 mg of prostigmine methylsulfate with 0.6 mg of atropine sulfate is given intramuscularly. Examination of muscular function is made thereafter every ten minutes for an hour. The presence and the amount of improvement in muscular strength are a great aid in making the diagnosis. One must be careful not to give the drug in cases of progressive muscular atrophy and amyotrophic lateral sclerosis, in which bulbar palsy might be precipitated with fatal results. They have found<sup>22</sup> that pregnancy generally causes an improvement in symptoms. Strickroot and his associates<sup>23</sup> report a case in which a mother with the disease gave birth to a myasthenic child. This is the first case reported, as far as I know, of direct inheritance of the disease, but it has been classified<sup>24</sup> among the instances of familial myopathy on the basis of the close relationship of the condition to the inheritable endocrine dyscrasias of the thymus and the thyroid. The recent surgical work just reported on makes this view more tenable, since it points to the possibility that myasthenia gravis is more a metabolic or endocrine than a neurologic disease. This concept is supported by the physiologic work of Harvey, Lilienthal and Talbot,<sup>25</sup> who have found electromyographic evidence that the disturbance in myasthenia is at the neuromuscular junction (motor end plates) and that the

19 Blalock, A., Harvey, A. M., Ford, F. R., and Lilienthal, J. L., Jr. Treatment of Myasthenia Gravis by Removal of Thymus Gland, *J. A. M. A.* **117** 1529 (Nov. 1) 1941.  
Blalock, A., Mason, M. F., Morgan, H. J., and Riven, S. S. *Ann. Surg.* **110** 544, 1939.

20 Cope, O. Personal communication to the author.

21 Schwab, R. S., and Viets, H. R. *New England J. Med.* **219** 226, 1938.

22 Viets, H. R., Schwab, R. S., and Brazier, M. A. B. Effect of Pregnancy on Course of Myasthenia Gravis, *J. A. M. A.* **119** 236 (May 16) 1942.

23 Strickroot, F. L., Schaeffer, R. L., and Bergo, H. L. Myasthenia Gravis Occurring in Infant Born of Myasthenic Mother, *J. A. M. A.* **120** 1207 (Dec. 12) 1942.

24 Aring, C., and Cobb, S. *Medicine* **14** 77, 1935.

25 Harvey, A. M., Lilienthal, J. L., Jr., and Talbot, S. A. *Bull. Johns Hopkins Hosp.* **69** 547, 1941.

disorder resembles that caused by curare. It could result from a deficiency in acetylcholine or an increase in the stimulation threshold of the end plates. Ayer<sup>26</sup> and Reese<sup>27</sup> have written comprehensive reviews of this subject.

#### CONFIRMATION OF FREUDIAN THEORIES

Many leaders in the fields of medicine, psychology, anthropology and sociology would accept the statement that Freud made the greatest contribution of his time to the study of personality. In medicine the study of personality has always been recognized as important, but in the last few years it has been emerging from the age-old stage of intuition and "common sense" to a level that at last is beginning to be scientific. It is beginning to be appreciated that interpersonal relations have a direct bearing on the problems of internal medicine and surgery as well as on those of psychiatry. Three recent books mark an advance in this field. Murray's "Exploration in Personality," 1938<sup>28</sup>, Rapaport's "Emotions and Memory," 1942,<sup>29</sup> and Sears's "Survey of Objective Studies of Psychoanalytic Concepts, 1943"<sup>30</sup>. All three of these books attempt to bring together psychoanalysis and experimental psychology. A recent editorial in *The Journal of the American Medical Association*<sup>31</sup> states that "the criteria for judging freudianism as a scientific contribution must be the same as those employed in judging any other scientific discipline." With this sound pronouncement I agree. The three books mentioned all contain sections which are attempts to evaluate freudian observation and theory by nonfreudian psychologic technics. Sears's monograph is frankly devoted to this object. Murray's book<sup>32</sup> is the first comprehensive attempt along this line. He says "Our work is the natural child of the deep, significant, metaphorical, provocative and questionable speculations of psychoanalysis and the precise, systematic, statistical, trivial and artificial methods of academic personology." Rapaport has investigated an important phase of repression.

The report<sup>30</sup> by the Social Science Research Council on Psychoanalytic Concepts is timely and important. It was prepared by Robert R. Sears, Professor of Child Psychology at the University of Iowa, for the Council's Committee on Social Adjustment. It is a book of 156 pages devoted to the appraisal of freudian theory by means of objective investigation, both observational and experimental (some by psychoanalysts, but much by investigators trained in other schools). As yet there have been only a few attempts to apply the experimental method. Some, however, are significant, and, as already suggested, every one interested in the field should agree that the freudian concepts must be tested by other than psychoanalytic methods before the theory can be accepted as fact. A start is being made in this direction.

The theory of repression is probably the most fundamental of Freud's concepts. Rapaport's book could be roughly described as an "investigation of repression," but this would be unfair, because he is careful to show that words must be exactly defined and fields delineated before a project is begun. He summarizes by saying<sup>29</sup>

Originally our problem was posed by the fact that in the taking of case-histories, clinical psychologists and psychiatrists and other medical men frequently find that the patient "forgets" to give what is obviously the most pertinent information, or unwittingly gives false replies

26 Ayer, J. B. *New England J. Med.* **228**: 422, 1943.

27 Reese, H. H., Lewis, N. D. C., and Sevringhaus, E. L. 1942 Year Book of Neurology, Psychiatry and Endocrinology, Chicago, Year Book Publishers, Inc., 1943.

28 Murray, H. A. *Exploration in Personality*, New York, Oxford University Press, 1938.

29 Rapaport, D. *Emotions and Memory*, Baltimore, Williams & Wilkins Company, 1942.

30 Sears, R. R. *Survey of Objective Studies of Psychoanalytic Concepts*, Bulletin 51, Committee on Social Adjustment, New York, Social Science Research Council, 1942.

31 *Psychoanalysis and the Scientific Method*, editorial, *J. A. M. A.* **122**: 811 (July 17) 1943.

32 Previously reviewed (*Arch. Neurol. & Psychiat.* **44**: 1152 [Dec.] 1940).

to crucial questions. These peculiar phenomena of "forgetting," as well as the generalized amnesias to which it was considered intimately related, were conceived and designated as being of an "emotional origin." Our task was to investigate whether and in what sense this is generally maintained, and what the basis of the assertion is.

The task comprised reviewing a large mass of literature and performing many special tests. The conclusion is that the processes of perception, memory and forgetting are closely connected with emotional feelings. The problem grew larger as the work proceeded, and why a person remembers certain events, why attention and interest are heightened, appears closely related to why one represses and forgets other events. Freud's theory is substantiated, but the problem is found to be wider, "emotions and memory" are found to encompass a large part of thinking.

The essence of Freud's idea of repression lies in the elimination from consciousness of all ideas or memories that might help to reactivate a painful anxiety. In addition to this primal sort of repression there is an associative amnesia, i. e. many memories entirely unrelated in content can be repressed simply because they had a time relation with the anxiety reaction created by parental punishment of strongly motivated behavior. Since sex behavior in children is one of the most consistently punished forms of action in Western civilization, sex is one of the most frequent sources of repression. By such a mechanism Freud explains the amnesia for most of the experiences of preschool years.

It is well known that an amnesia something like that postulated in the theory of repression can be induced by hypnosis. The phenomena of posthypnotic suggestion in which a person performs some foolish act some time after awakening from the hypnotic state and has no idea why he does the act certainly show that mental processes can be made subconscious and can continue to act at that level. No experiments, however, seem to throw much light on repression itself and whether anxiety and unpleasantness are factors in its induction. Such data as there are suggest that unpleasantness interferes with memory. The theory that amnesia for events occurring before the age of 5 years is due to repression is controverted by some investigations<sup>33</sup> which show clearly that learning functions in infants are not well developed, the memorizing process is poor at this age and parallels the poor recall for infantile experiences.

The libido theory postulates that all drives to emotional relations with others are, broadly speaking, sexual in origin. In short, love and hate of all types are libidinal. Few persons would doubt the validity of the generalization after contemplating the differences between the bull and the ox. The theory carries with it, however, the corollary that the infant must have libido at birth and that sexual behavior must begin in earliest infancy. It was this idea of infantile sexuality which brought down on Freud's head the greatest storm of criticism. This is easily explained by the cultural attitude toward sex in Europe thirty years ago. Since then observations on infants and nursery school children have recorded "such a tremendous number of instances of behavior organized around oral, anal, urethral and genital functions and ideas that Freud may be freed forevermore of any charge of overestimating the frequency of such behavior."<sup>30</sup> Nevertheless it must be remembered that Freud did not work with children, he got his data largely from psychoneurotic adults who recalled and reported to him their childhood behavior. These clinical data were slowly amassed and eventually led to the description of infantile libidinal development as first oral, then anal and urethral and finally genital. Malinowski's<sup>31</sup> work, however, shows that genital play occurs very early in certain savage tribes among whom it is not repressed.

<sup>33</sup> Child, I. L. *J. Abnorm. Psychol.* **35** 453, 1940.

<sup>34</sup> Malinowski, B. *Psychoanal. Rev.* **14** 20, 1927.

Worry over sex differences, fear of losing the penis by boys ("castration complex") and a desire to have a penis among girls ("penis envy") are also psychoanalytic observations considered important in determining later behavior. These phenomena certainly occur, but Freud's belief that they were practically universal has not been backed up by any subsequent work. Few psychiatrists doubt that the complex has affected certain neurotic adults, and many child psychologists have seen obvious examples of the fear in children from 2 to 5 years old, especially those that have been subjected to surgical treatment. Nevertheless no data are given in the psychoanalytic literature that show how often the fear occurs in anxious children or in normal children. Conn<sup>35</sup> made an attempt with "play technic" to find out how often children are emotionally upset by learning about the sex difference between boys and girls, and found evidence that about 8 per cent were disturbed by the problem. Surveys of adult sex behavior, however, have shown that adequate early sex instruction is correlated with adequate orgasm in women, poorly instructed women are more likely to be frigid. What is needed is many more data from direct observation of children. Only from such observations can answers be given to the questions: When and how shall I instruct my child about sexual differences? Is "fear of castration" in boys universal, common or rare? Is it universal; common or rare for girls to envy boys their male genital development? There is plenty of evidence that these questions are important in neurotic developments. Whether or not they are of importance to sociology and anthropology is for future work to decide. At present it looks as if Freud's postulates were too broad and should be applied only to "Western European culture" and perhaps only to neurotic persons in that culture.

Freud's clinical observations that sexual perversions arise from mixed and opposing impulses and are commonly multiple are strongly corroborated by others<sup>36</sup>. Perversions are much more common than is usually believed, and they are usually related to lack of orgasmal adequacy. The pervert, then, is not "hypersexed" in the ordinary sense, it seems that he is often obsessed with sex (and thereby overactive in that line) because of lack of normal satisfaction. A large number of persons with perverted impulses recall childhood satisfactions from the anal, urethral and oral zones. This gives some substantiation to the psychoanalytic theory that excessive preoccupation with stimulation of these zones before the development of genital sexuality may predispose a child to later development of perversion.

Quite different from the simpler anal satisfactions and interests common to most infants and many adults is the "anal eroticism" recognized by Freudians. This consists in pleasure arising from stimulation of the rectal mucous membrane due to retained feces. There is also pleasure when the retained mass is expelled, stretching and stimulating the rectum. A complex theory has arisen about this form of pleasure, that it leads to the "anal character," the cardinal attributes of which are orderliness, stinginess and obstinacy. Sears points out that some psychologic investigations show that these traits tend to go together but that there is no evidence, except the psychoanalytic observations on neurotic patients, that show the relationship of these character traits to the "anal erotic" syndrome. Sadism is said to be related to the anal character, but surveys by nonpsychoanalytic methods indicate that masochism is almost as common. It is probable, then, that Freud's statements about the polymorphism of perversity are correct and that patients with anal interests form a neurotic group, but there is no good confirmatory

35 Conn, J. H. *Am J Orthopsychiat* 10 747, 1940

36 Terman, L. M. *Psychological Factors in Marital Happiness*, New York, McGraw-Hill Book Company, Inc., 1938. Sears<sup>30</sup>

evidence that orderly, stingy and obstinate people are either "anal erotic" or sadistic. Two surveys by psychologists indicate that paranoid patients have a much higher incidence of homosexuality than other psychotic groups. Also there are clinical data indicating that alcoholism may often be related to homosexual trends. Both of these observations support findings of Freud. It is obvious that there is need now for more good observation of children's eliminative and sexual habits with follow-up for years, to prove or disprove the Freudian theories.

The direction in which a person discharges his love and hate is certainly of great importance. As a child he directs it toward other persons, later, toward more abstract objects. This choice of the object for emotional discharge has been called "cathexis" by Freud (taking the electrical term because of its value as a simile). The theory of cathexis does not need confirmation, because it is a redefinition of a phenomenon which is accepted as common knowledge. The subordinate phenomena can be examined critically.

The sequence of events in the choice of love objects is of prime importance in psychoanalytic theory. It is briefly as follows. The first genital sexuality is homoerotic, the child explores himself and is interested in himself. Observation of infants amply corroborates this simple sort of "narcissism." Love is also turned toward the mother because of her nursing and tending activities. Between 6 and 8 years of age the child inhibits this direct mother attachment, and the "latency period" sets in and goes on until he is 10 or 12 years of age, when puberty brings on heterosexual interests. The "oedipus situation" is deep attachment of a boy for his mother (which is inhibited because of fear of the father), there is a less well defined situation in the love of a daughter for the father. Workers in psychiatry and psychology using other than Freudian methods have amply confirmed the occurrence of this sequence of events in many cases. There is, however, no proof that it is typical or the rule. In fact, anthropologists<sup>31</sup> have evidence that in primitive races genital development begins early and goes on steadily through adolescence, showing no signs of a latency period and no oedipus situation. Certain psychologic surveys, notably that of Bell<sup>37</sup> on midwestern children in the United States, corroborate the existence of a latency period in "Western civilization" whereas others reviewed by Sears do not find evidence of it. Cathexis is a useful psychologic concept, but the pattern varies so greatly with the cultural pattern and is so bound up with the process of learning by experience that Freud's interpretation is too narrow. There is good evidence that it applies to European culture and gives a good explanation for certain types of neurosis. Homosexuality seems to be not infrequently related to a strong mother attachment.

Sears pays particular attention to "fixation" and "regression." It was observed by Freud that certain patients who had reached a normal heterosexual adjustment returned to earlier modes of satisfaction. A man might be frustrated in his attempt to adjust in an adult way to his wife and revert to a childish attempt to get mothering. This would be "regression" caused by "frustration", "fixation" of affection on a love object is a prerequisite for such frustration. Reactions like the example given are commonly recognized, psychoanalysts consider the mechanism of regression a good explanation for much neurotic and even schizophrenic behavior. Sears's review describes much careful experimental work. He concludes

The success with which animal psychologists have attacked fixation and regression is dimmed somewhat by the fact that experimental regression is not entirely representative of the Freudian clinical phenomenon. There is sufficient systematic relation between them, however, to suggest that most of the experimental findings can be applied safely to the latter.

37 Bell, S. *Am J Psychol* 13 325, 1902



If fixation is defined as an unusually strong object attachment, or instrumental act, regression can be considered as the reactivation of a fixated but previously relinquished response following the weakening of a later established response. The weakening, as has been shown, can be secured through frustration by punishment, frustration by removal or reward, satisfaction or alcohol. When the ongoing response is weakened by any of these four factors, other responses become prepotent, and if the ensuing response is one that was strong at some earlier date, the change in behavior is called regression. These experimental findings give sound support to Freud's contention that regression is a function of fixation, and they suggest that his notion of the importance of frustration is correct as far as it goes but is not the only factor that can give opportunity for fixation to play its role.

This discussion of repression, libido, infantile sexuality, perversion and regression gives examples of the way in which Freud's postulates are now being examined by psychologists and psychiatrists by nonfreudian technics. One might summarize by saying that these workers have found some confirmation for the libido theory, infantile sexuality, the "castration complex," the polymorphism of perversion, and repression and regression. They have found evidence against accepting the subdivisions of infantile sexuality as characteristic of children in general, against the theory of anal eroticism and its effect on character, and against using such concepts as the "castration complex" and "penis envy" except in a limited way for certain cultural areas. Also there is good evidence against the theory of infantile repression. More work should be done along these lines, for the work sketched in the foregoing paragraphs is spotty and little of it follows a program, with the obvious exceptions of Murray's and Rapaport's monographs. One must admit that it looks as if Freud made some remarkably shrewd generalizations from his clinical observation of human nature.<sup>1</sup> It is important to know which generalizations are true and which are false, and this can be determined only by future research along the lines indicated.

#### SHOCK THERAPY

The hopes of 1938, when insulin shock therapy was at its height, have vanished. Sound psychiatrists reviewing the situation at present show much less enthusiasm for any of the shock treatments. For example, Rennie<sup>38</sup> says:

The tested methods of psychiatry and psychotherapy are still important, and the most important methods available. The procedure in shock therapy, because of its hazards, belongs in the hands of thoroughly trained physicians and should be limited to hospital practice, not office or consultation routine. No convincing rationale for therapy has yet emerged. There are dangers to be encountered, to life and to the mental performance of the sufferer. These cannot be shoved aside.

The use of insulin, except as an aid for relieving certain symptomatic manifestations of schizophrenia, is largely discarded. In fact, some workers<sup>39</sup> have published series of cases with controls that show insulin therapy to be no better in its results than the former types of conservative hospital care. While insulin shock therapy was at its height, the use of metrazol shock came in. This type of treatment was easier to employ and had more dramatic effects. At first hopes were raised that here was a cure for schizophrenia, but they were soon disappointed when it appeared that the only patients benefited with any regularity were the ones with depressions. Metrazol, however, caused such brutal convulsions, with so many fractures and so much terror in the patients, that it never was as much used as its quick successor, electric shock. This method of treatment is now sweeping the field of therapy in neuropsychiatry, and a warning against indis-

38 Rennie, T. A. C. *Psychiatry* 6:127, 1943.

39 Gootlieb, J. S., and Huston, P. E. Treatment of Schizophrenia. Follow-Up Results in Cases of Insulin Shock Therapy and in Control Cases, *Arch. Neurol. & Psychiat.* 49:266 (Feb.) 1943.



criminate use is needed. In the hands of careful physicians the electrical shocking machines have given good results in shortening the depressions of the manic-depressive psychoses and in relieving the chronic agitated-depressive states of the involutional period. Also the outward behavior of schizophrenic patients is often changed for the better. Many data have been amassed, and a symposium on the subject was held at the last meeting of the American Psychiatric Association.<sup>40</sup> In general, the results in 1943 corroborate the preliminary impression given by reports in 1941.<sup>41</sup> Involutional melancholia is usually benefited, other depressions seem to be shortened in a majority of cases, manic states are improved in about half the patients treated, and the method is of no use for the neuroses.

Electric shock is easily given, dramatic to the family and relatively pleasant for the patient, because it leaves him with an amnesia, so that he does not mind having had the fit (unless he happens to be one of the 3 to 5 per cent that suffer a fracture or dislocation). These facts are all to the good, but the difficulty is that they play too easily into the hands of the enthusiastic therapist and the charlatan. Electric shock, unfortunately, is being used indiscriminately for all sorts of nervous and mental troubles, from anxiety states, which could be relieved by psychotherapy, to multiple sclerosis, for which its use is obviously a stupid counsel of despair.

Another aspect of electric shock treatment must be discussed. The anatomic and physiologic effects on the brain of electricity, currents such as those used in this therapy, are not known. The investigators do not agree,<sup>42</sup> and the investigations are inadequate. Since the therapists do not yet know what they are doing to the brain by electroshock, it certainly is only common prudence to go slowly, use as few shocks as possible and make careful examination of the patient's mental state, especially memory, before and after treatment. Such procedure is certainly followed by the careful and well trained men who use the method. The less discriminative shockers, however, do not seem to fear the possibly permanent intellectual defects that may occur from repeated electrical convulsions. In hospitals it has been found that many disturbed and active patients can be made quieter by repeated shock treatments. Their behavior is so much improved that nursing is simplified. Some of them look, however, as if they had been partially decorticated. I feel it imperative to repeat what I said in 1939.<sup>43</sup> "One feels doubtful of the ethical standards that allow shock treatment to be given for the purpose of making nursing easier for the hospital administration. It comes dangerously close to punishment, and logically one might ask 'Why not euthanasia?'"

Massachusetts General Hospital

40 Am J Psychiat, to be published

41 Cobb, S. Review of Neuropsychiatry for 1941, Arch Int Med 68 1232 (Dec) 1941

42 Globus, J. H., van Harreveld, A., and Wiersma, C. A. G. J Neuropath & Exper Neurol 2 263, 1943. Hassin, G. B. Cerebral Changes in Fatal Cases Following Treatment with Barbitol, Soluble Barbitol U. S. P., Insulin and Metrazol, Arch Neurol & Psychiat 42 679 (Oct) 1939

43 Cobb, S. Review of Neuropsychiatry for 1939, Arch Int Med 64 1328 (Dec) 1939

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